

ROBBINS

# Basic Pathology

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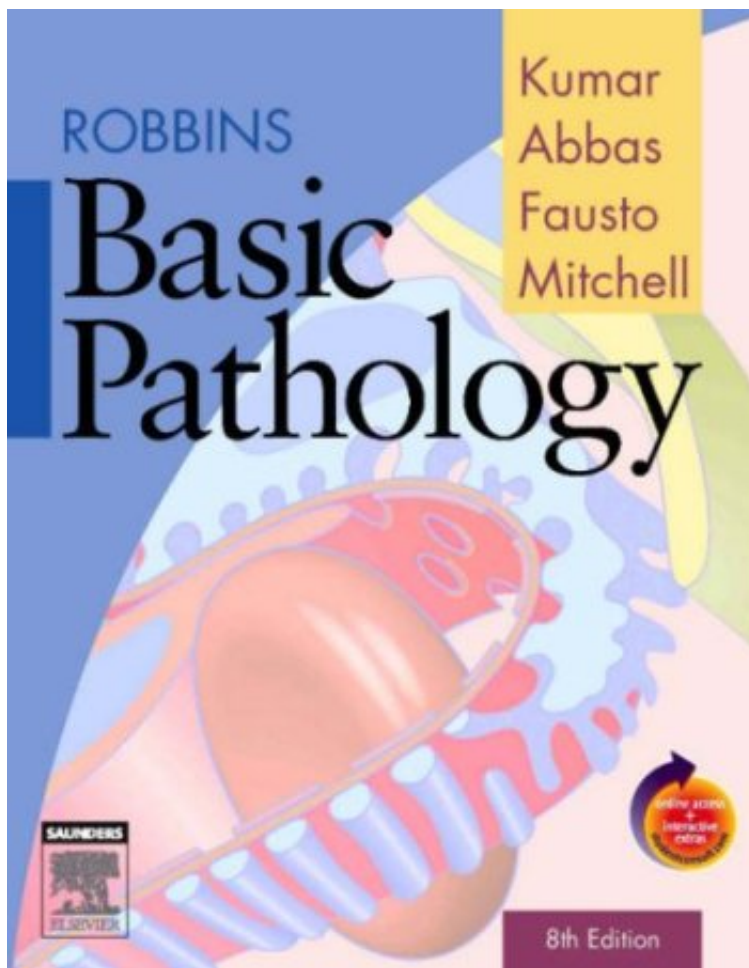


8th Edition





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## 1 Cell Injury, Cell Death, and Adaptations

### INTRODUCTION TO PATHOLOGY

Literally translated, *pathology* is the study (*logos*) of suffering (*pathos*). It is a discipline that bridges clinical practice and basic science, and it involves the investigation of the causes (*etiology*) of disease as well as the underlying mechanisms (*pathogenesis*) that result in the presenting signs and symptoms of the patient. Pathologists use a variety of molecular, microbiologic, and immunologic techniques to understand the biochemical, structural, and functional changes that occur in cells, tissues, and organs. To render diagnoses and guide therapy, pathologists identify changes in the gross or microscopic appearance (*morphology*) of cells and tissues, and biochemical alterations in body fluids (such as blood and urine). Traditionally, the discipline is divided into general pathology and systemic pathology; the former focuses on the fundamental cellular and tissue responses to pathologic stimuli, while the latter examines the particular responses of specialized organs. In this book we first cover the broad principles of general pathology and then progress to specific disease processes in individual organs.





## INTRODUCTION TO PATHOLOGY

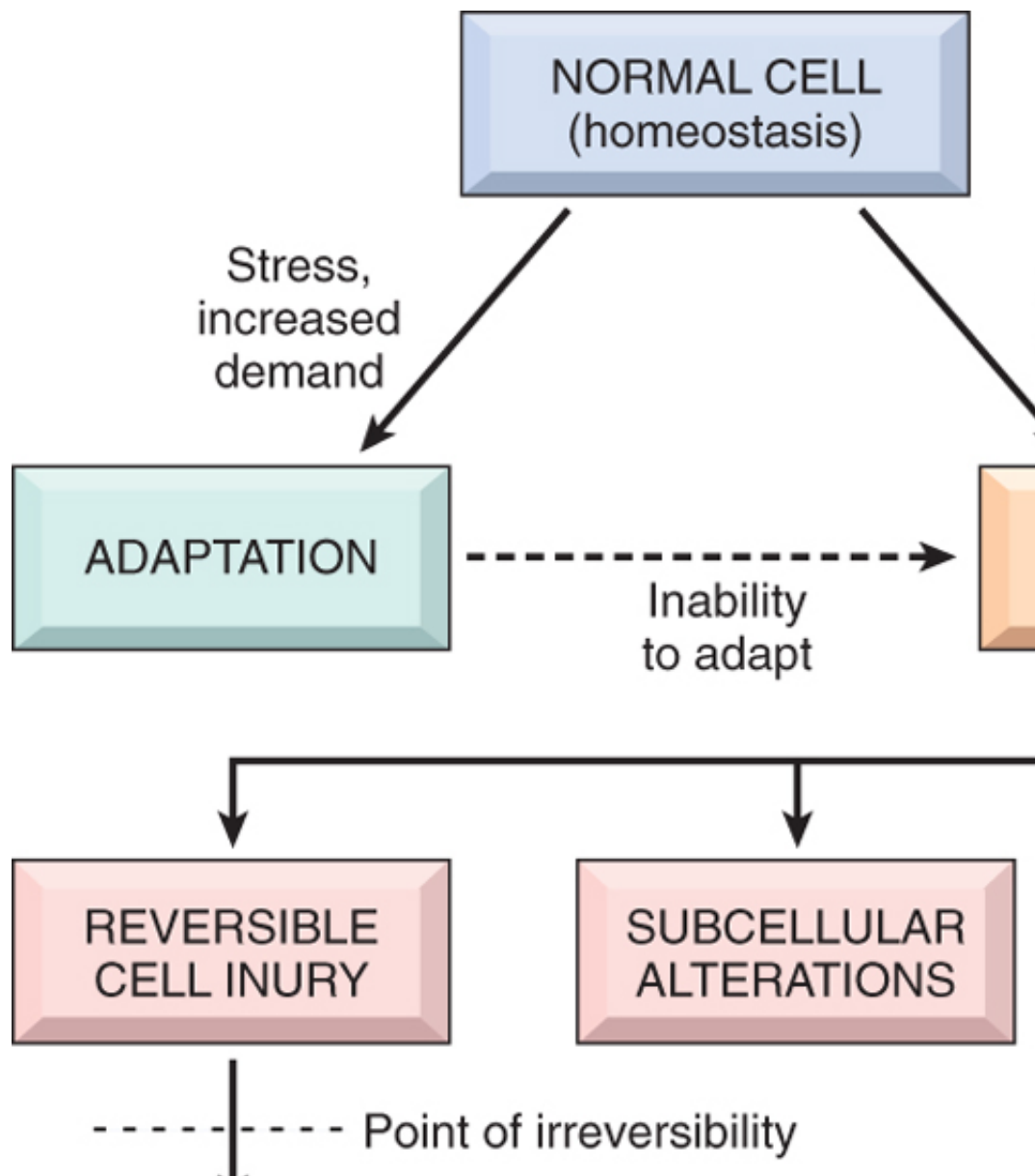
Literally translated, *pathology* is the study (*logos*) of suffering (*pathos*). It is a discipline that bridges clinical practice and basic science, and it involves the investigation of the causes (*etiology*) of disease as well as the underlying mechanisms (*pathogenesis*) that result in the presenting signs and symptoms of the patient. Pathologists use a variety of molecular, microbiologic, and immunologic techniques to understand the biochemical, structural, and functional changes that occur in cells, tissues, and organs. To render diagnoses and guide therapy, pathologists identify changes in the gross or microscopic appearance (*morphology*) of cells and tissues, and biochemical alterations in body fluids (such as blood and urine). Traditionally, the discipline is divided into general pathology and systemic pathology; the former focuses on the fundamental cellular and tissue responses to pathologic stimuli, while the latter examines the particular responses of specialized organs. In this book we first cover the broad principles of general pathology and then progress to specific disease processes in individual organs.





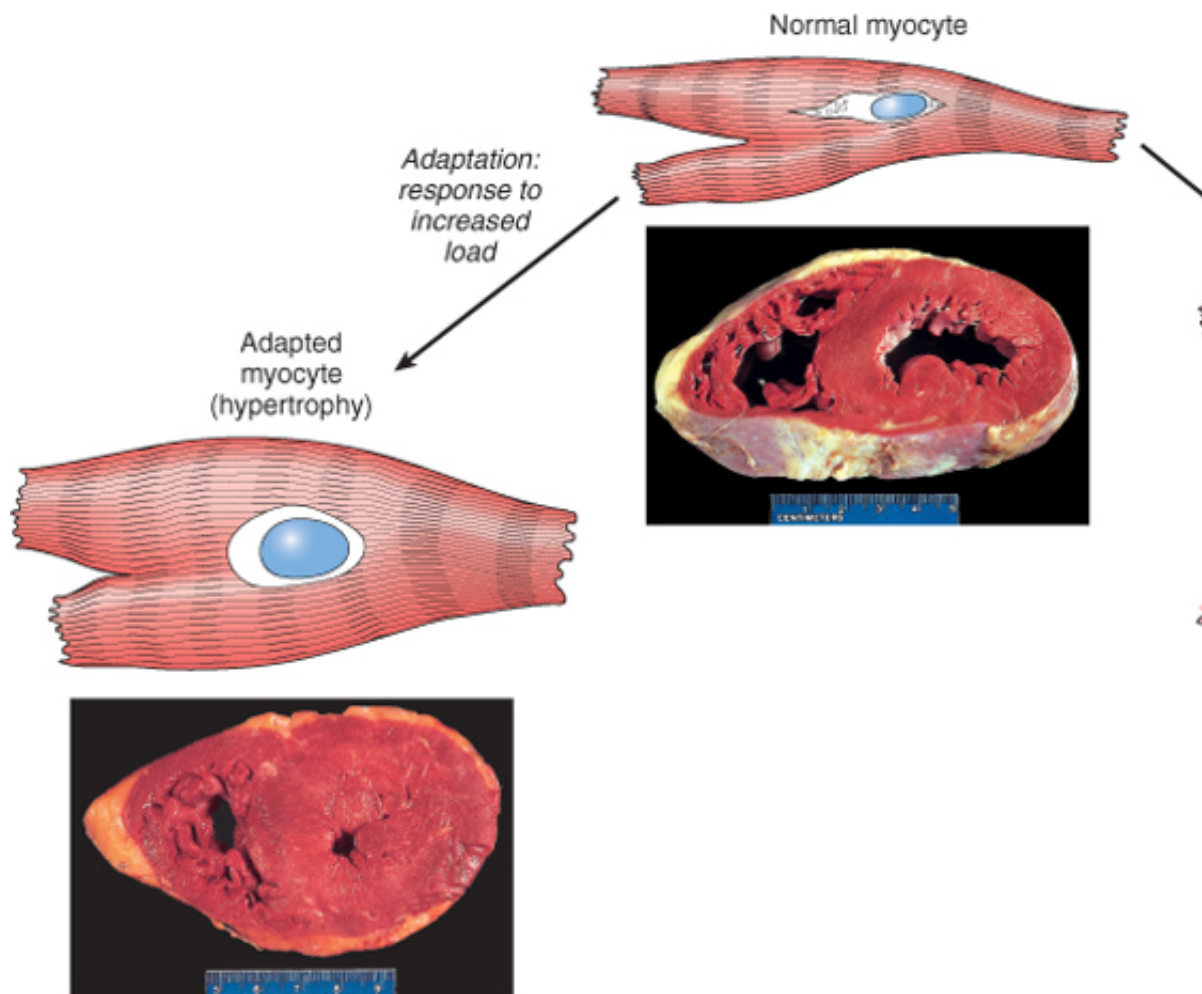
## OVERVIEW OF CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI

Cells are active participants in their environment, constantly adjusting their structure and function to respond to extracellular stresses. Cells tend to maintain their intracellular milieu within a fairly narrow range to maintain normal *homeostasis*. As cells encounter physiologic stresses or pathologic stimuli, they attempt to maintain a steady state and preserving viability and function. The principal adaptive responses are *hypertrophy* and *hyperplasia*. If the adaptive capability is exceeded or if the external stress is inherently harmful, *cell injury* develops. If the injury is *reversible*, and cells return to a stable baseline; however, severe or persistent stress results in *irreversible cell injury* and *cell death*. *Cell death* is one of the most crucial events in the evolution of disease in any tissue, including ischemia (lack of blood flow), infections, toxins, and immune reactions. Cell death is also involved in embryogenesis, the development of organs, and the maintenance of homeostasis.



# ▼ NECROSIS

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Figure 1-1 Stages in the cellular response to stress and injurious stim



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Figure 1-2 The relationship between normal, adapted, reversibly injured, and dead myocardial cells. The cellular ad reversible injury is ischemia, and the irreversible injury is ischemic coagulative necrosis. In the example of myoca wall is thicker than 2 cm (normal, 1-1.5 cm). Reversibly injured myocardium shows functional effects without any c changes like cellular swelling and fatty change (shown here). In the specimen showing necrosis (*lower right*) the ventricle represents an acute myocardial infarction. All three transverse sections of myocardium have been stain substrate that colors viable myocardium magenta. Failure to stain is due to enzyme l

The relationships between normal, adapted, and reversibly and irreversibly injured cells are well il different types of stress (Fig. 1-2). Myocardium subjected to persistent increased load, as in hyper by undergoing *hypertrophy*-an increase in the size of the individual cells and ultimately the entire l contractile force. If the increased demand is not relieved, or if the myocardium is subjected to red



occluded coronary artery, the muscle cells may undergo injury. Myocardium may be reversibly injured if occlusion is incomplete or sufficiently brief, or it may undergo irreversible injury (*infarction*) after a longer period. In addition, stresses and injury affect not only the morphology but also the functional status of cells. Although myocytes are not dead and may resemble normal myocytes morphologically; however, they are not functional. Even mild injury can have a lethal clinical impact. Whether a specific form of stress induces adaptive or injurious changes depends not only on the nature and severity of the stress but also on several other variables: oxygen supply, and nutritional status.

In this chapter we discuss first how cells adapt to stresses and then the causes, mechanisms, and consequences of acute cell damage, including reversible cell injury, subcellular alterations, and cell death. We conclude with a discussion of chronic diseases that affect cells and tissues: intracellular accumulations, pathologic calcification, and cell aging.



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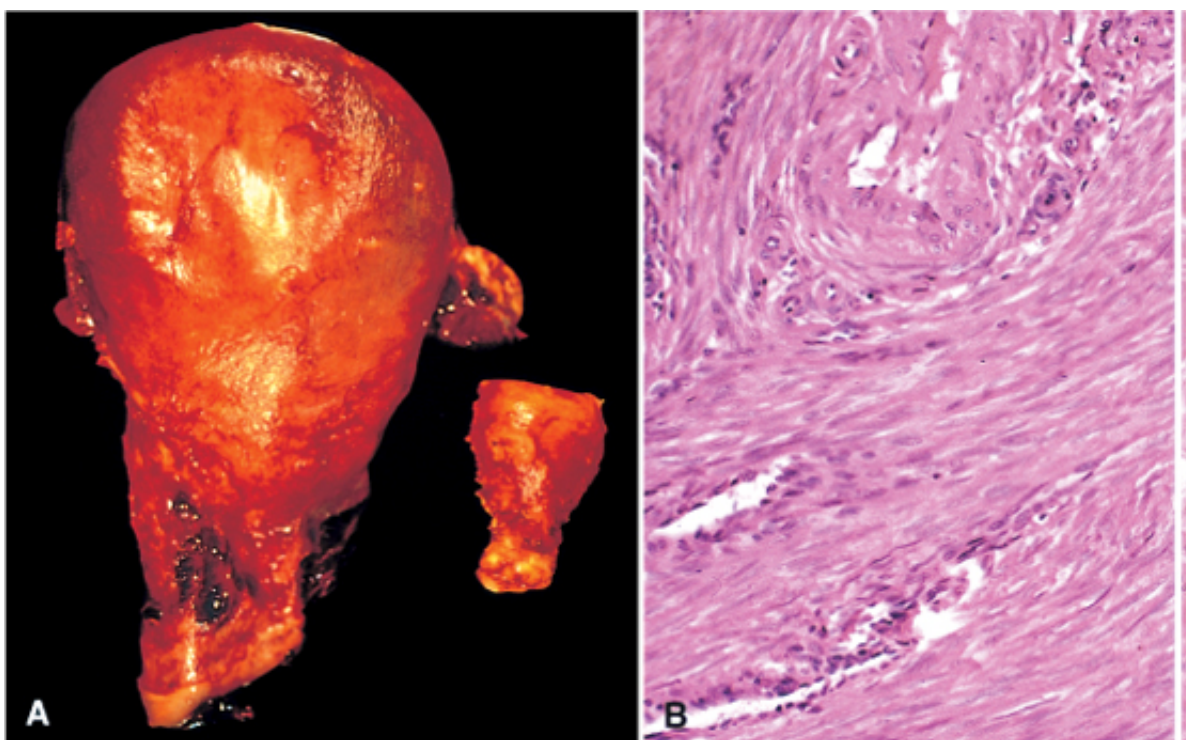


## CELLULAR ADAPTATIONS TO STRESS

Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or function environment. *Physiologic adaptations* usually represent responses of cells to normal stimulation by mediators (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy). *Pathologic adaptations* are stress that allow cells to modulate their structure and function and thus escape injury. Such adaptations

### Hypertrophy

*Hypertrophy is an increase in the size of cells resulting in increase in the size of the organ.* In contrast to hyperplasia, which is characterized by an increase in cell number. Stated another way, in pure hypertrophy there are not an increased amount of structural proteins and organelles. Hyperplasia is an adaptive response in which cell division occurs. Hypertrophy occurs when cells are incapable of dividing. *Hypertrophy can be physiologic or pathologic.* Hypertrophy can be induced by functional demand or by specific hormonal stimulation. Hypertrophy and hyperplasia can also occur together to form an enlarged (*hypertrophic*) organ. Thus, the massive physiologic enlargement of the uterus during pregnancy is due to estrogen-stimulated smooth muscle hypertrophy and smooth muscle hyperplasia (Fig. 1-3). In contrast, skeletal muscle and the heart can undergo only hypertrophy in response to increased demand because they lack the capacity to divide. Therefore, the avid weightlifter can develop a rippled physique only by hypertrophy induced by an increased workload. Examples of pathologic cellular hypertrophy include the cardiac hypertrophy in hypertension or aortic valve disease (see Fig. 1-2).



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Figure 1-3 Physiologic hypertrophy of the uterus during pregnancy. **A**, Gross appearance of a normal uterus (right postpartum bleeding). **B**, Small spindle-shaped uterine smooth muscle cells from a normal uterus. Compare this with cells from a gravid uterus (**B** and **C**, same magnification).

The mechanisms driving cardiac hypertrophy involve at least two types of signals: *mechanical triggers*, such as activation of  $\alpha$ -adrenergic receptors. These stimuli turn on signal transduction pathways

...iggers, such as activation of a contractile receptor, these common pathways signal an increase in the number of genes, which in turn stimulate synthesis of numerous cellular proteins, including growth factors. The result is the synthesis of more proteins and myofilaments per cell, which achieves improved performance under demand and the cell's functional capacity. There may also be a switch of contractile proteins from one form to another. For example, during muscle hypertrophy, the  $\alpha$ -myosin heavy chain is replaced by the  $\beta$  form of the myosin, which allows for a more energetically economical contraction. Whatever the exact mechanisms of hypertrophy, a limit is reached. Further enlargement of muscle mass can no longer compensate for the increased burden. When this happens, regressive changes occur in the myocardial fibers, of which the most important are fragmentation and loss of myofibrils. These variables that limit continued hypertrophy and cause the regressive changes are incompletely understood. They include inadequate vasculature to adequately supply the enlarged fibers, of the mitochondria to supply adenosine triphosphate (ATP) for the machinery to provide the contractile proteins or other cytoskeletal elements. The net result of these changes is ultimately cardiac failure, a sequence of events that illustrates how *an adaptation to stress can prove maladaptive if the stress is not relieved*.

## Hyperplasia

As discussed above, hyperplasia takes place if the cell population is capable of replication; it may occur in response to the same stimuli.

Hyperplasia can be physiologic or pathologic.

The two types of *physiologic hyperplasia* are (1) *hormonal hyperplasia*, exemplified by the increase in the number of cells in the female breast at puberty and during pregnancy; and (2) *compensatory hyperplasia*, in which a portion of the tissue is removed or diseased. For example, when a liver is partially resected, compensatory hyperplasia begins as early as 12 hours later, eventually restoring the liver to its normal weight. The stimulation is by polypeptide growth factors produced by remnant hepatocytes as well as nonparenchymal cells. When the liver mass, cell proliferation is "turned off" by various growth inhibitors (Chapter 3). Most forms of hyperplasia are caused by excessive hormonal or growth factor stimulation. For example, after a normal menstrual cycle, there is a brief period of epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormone and inhibition through progesterone. However, if the balance between estrogen and progesterone is disrupted, hyperplasia ensues, a common cause of abnormal menstrual bleeding. Hyperplasia is also seen in wound healing, in which proliferating fibroblasts and blood vessels aid in repair. Growth factors are produced by white blood cells (leukocytes) responding to the injury and by cells in the wound. Growth factors is also involved in the hyperplasia that is associated with certain viral infections, such as skin warts and mucosal lesions composed of masses of hyperplastic epithelium. Here the growth is stimulated by virus or by infected cells. It is important to note that in all these situations, the hyperplastic response is reversible. When the growth factor stimulation abates, the hyperplasia disappears. It is this sensitivity to normal growth control that distinguishes benign pathologic hyperplasias from cancer, in which the growth control mechanism is ineffective (Chapter 6). Nevertheless, pathologic hyperplasia constitutes a fertile soil in which cancer can arise. Thus, patients with hyperplasia of the endometrium are at increased risk of developing cancer. Papillomavirus infections predispose to cervical cancers (Chapter 19).

## Atrophy

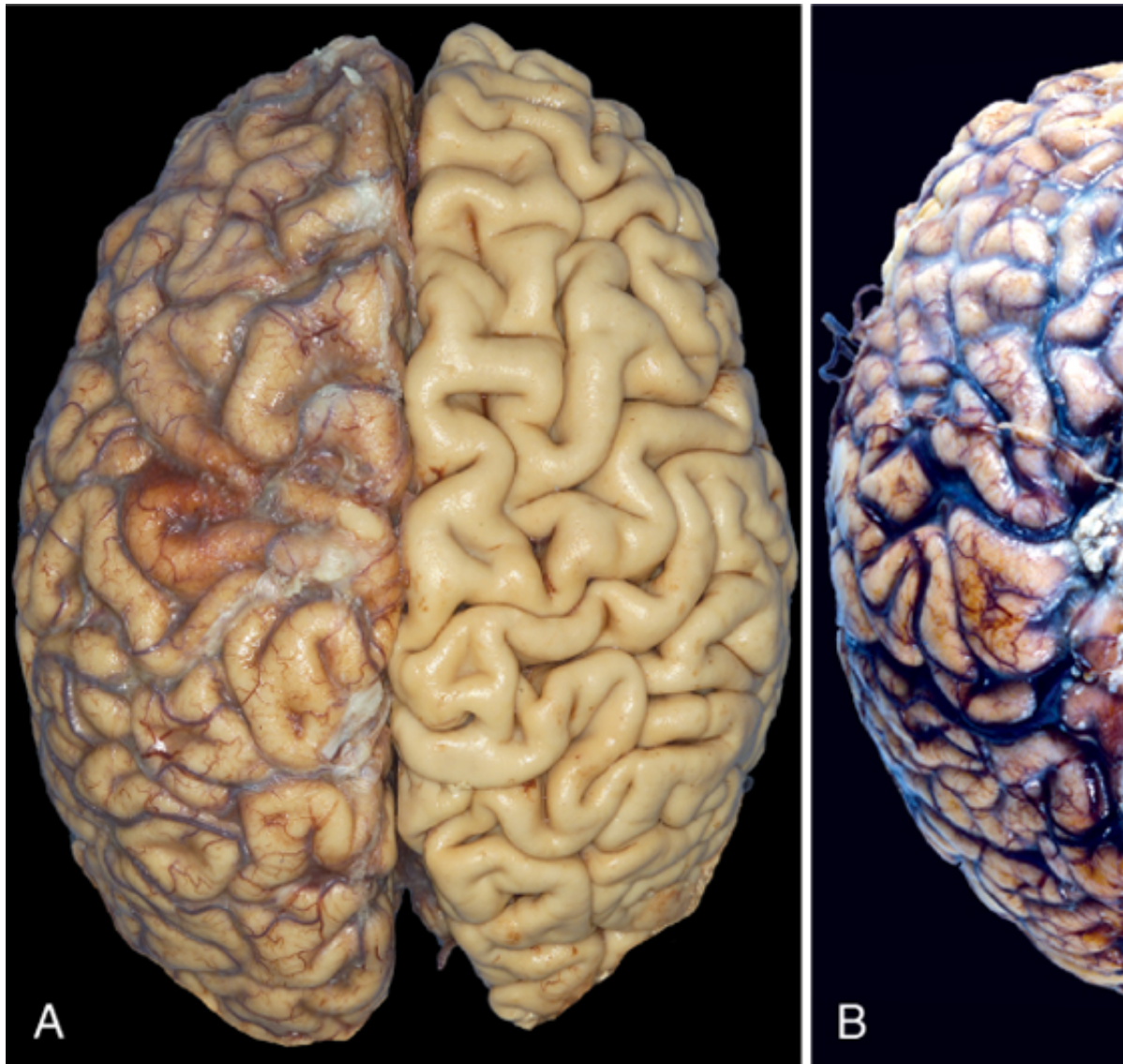
*Shrinkage in the size of the cell by the loss of cell substance is known as atrophy*. When a sufficient amount of tissue or organ diminishes in size, becoming atrophic (Fig. 1-4). It should be emphasized that *although the size is diminished, the cells are not dead*.

Causes of atrophy include a decreased workload (e.g., immobilization of a limb to permit healing) or a diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging (senile atrophy). Atrophy can be physiologic (e.g., the loss of hormone stimulation in menopause) and others pathologic (e.g., denervation). The changes are identical. They represent a retreat by the cell to a smaller size at which survival is still possible. Atrophy is reversible. Between cell size and diminished blood supply, nutrition, or trophic stimulation.

Atrophy results from decreased protein synthesis and increased protein degradation in cells. Protein synthesis is reduced by decreased metabolic activity. The degradation of cellular proteins occurs mainly by the ubiquitin-proteasome pathway. Ubiquitin is a small peptide that may activate ubiquitin ligases, which attach multiple copies of the small peptide ubiquitin to proteins. This process marks proteins for degradation by the proteasome.

proteins for degradation in proteasomes. This pathway is also thought to be responsible for the anorectic catabolic conditions, including cancer cachexia.

In many situations, atrophy is also accompanied by increased *autophagy*, with resulting increases in autophagy ("self-eating") is the process in which the starved cell eats its own components in an attempt to survive. We will describe this process later.



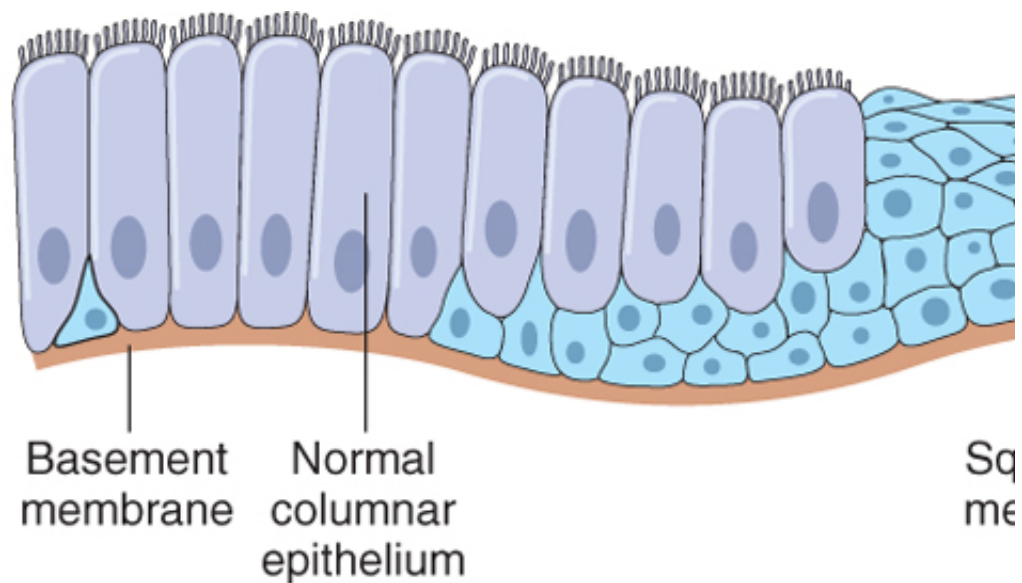
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Figure 1-4 Atrophy. **A**, Normal brain of a young adult. **B**, Atrophy of the brain in an 82-year-old male with atherosclerosis and reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges are removed from the specimen to reveal the surface of the brain.

## Metaplasia

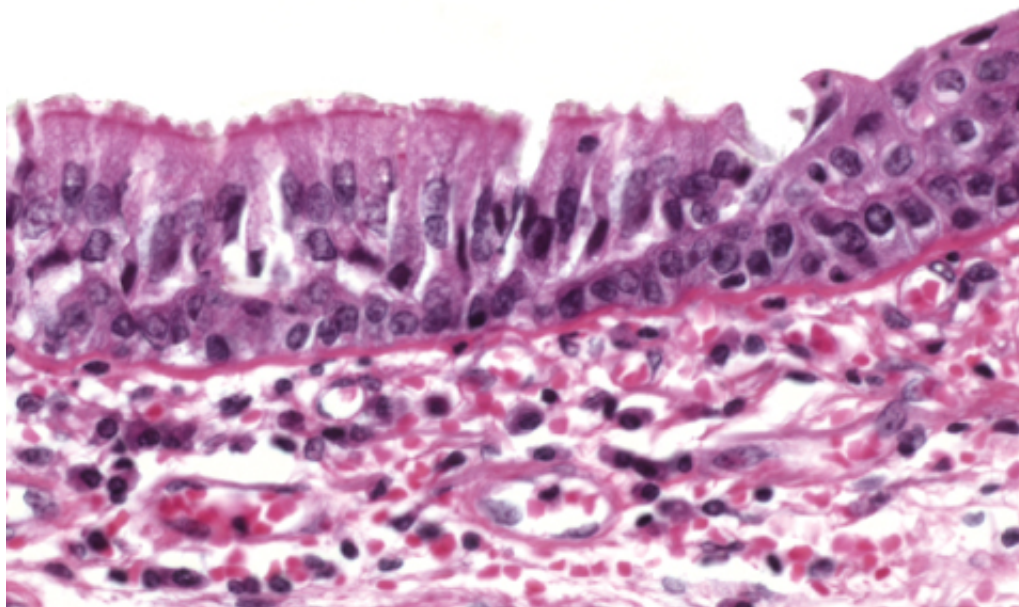
Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another cell type as an adaptation to a particular stress. Cells sensitive to a particular stress are replaced by other cell types better adapted to the environment. Metaplasia is thought to arise by genetic "reprogramming" of stem cells rather than by replacement of differentiated cells.



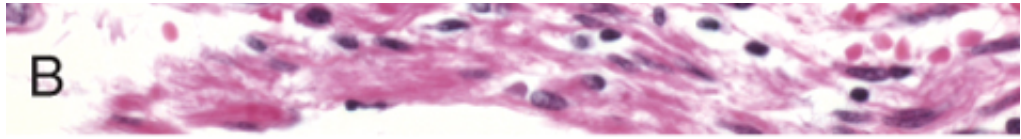
Epithelial metaplasia is exemplified by the squamous change that occurs in the respiratory epithelium (Fig. 5). The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by squamous cells. Vitamin A deficiency may also induce squamous metaplasia in the respiratory epithelium. The squamous epithelium may be able to survive under circumstances that the more fragile specialized epithelium cannot. *Metaplastic squamous epithelium has survival advantages, important protective mechanisms are the clearance of particulate matter.* Epithelial metaplasia is therefore a double-edged sword; moreover, *if persistent, may predispose to malignant transformation of the epithelium.* In fact, squamous metaplasia of the respiratory epithelium often coexists with cancers composed of malignant cells. Cigarette smoking initially causes squamous metaplasia, and cancers arise later in some of these. The transformation occurs in the direction of columnar to squamous epithelium; in chronic gastric reflux, the normal stratified columnar epithelium of the esophagus may undergo metaplastic transformation to gastric or intestinal-type columnar epithelium. This transformation is less clearly an adaptive response. For example, bone is occasionally replaced by cartilage after injury.



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 Figure 1-5 Metaplasia of normal columnar (*left*) to squamous epithelium (*right*) in a bronchus, shown (A)

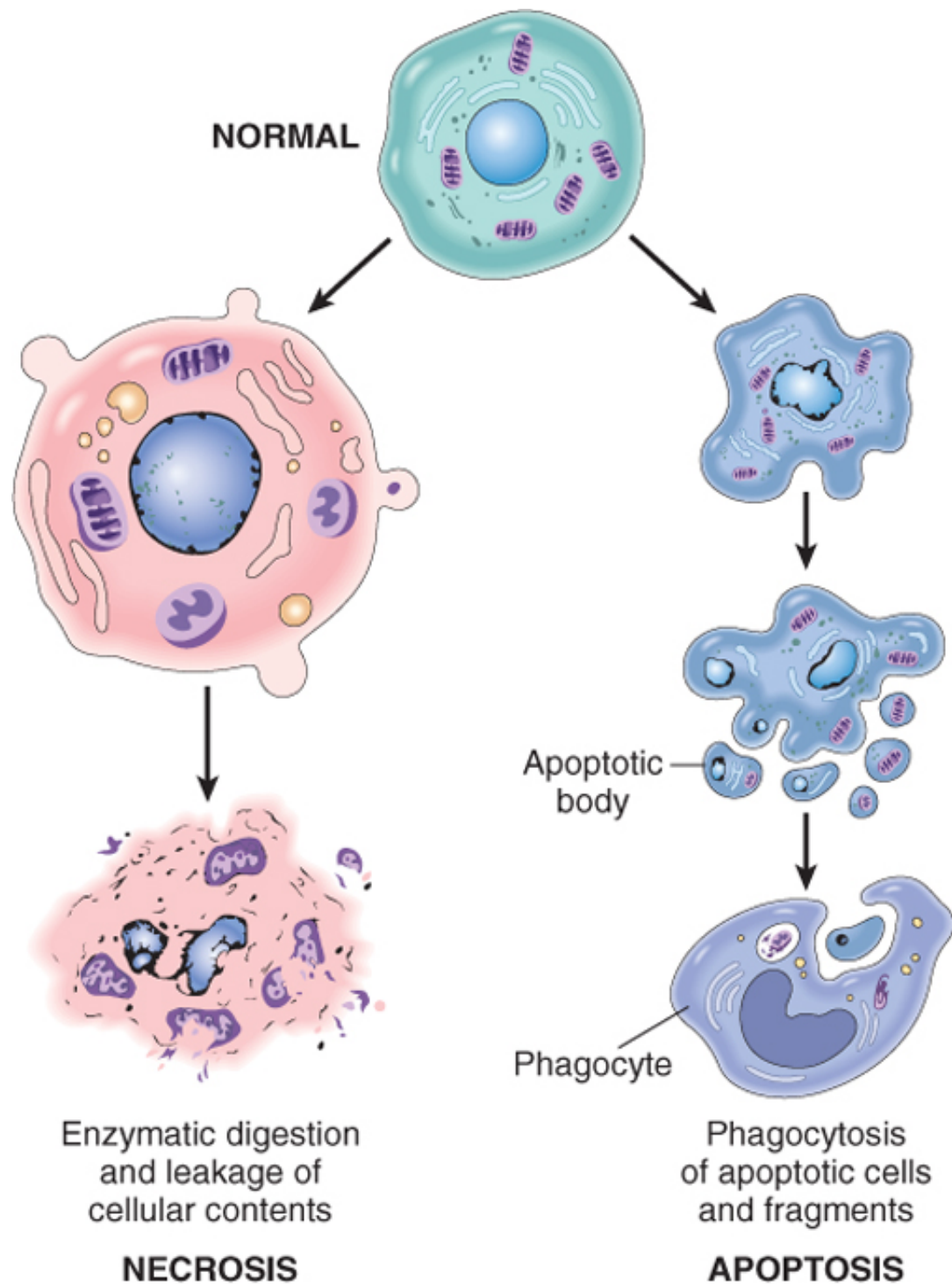
## SUMMARY

### Cellular Adaptations to Stress

*Hypertrophy*: increased cell and organ size, often in response to increased mechanical stress and by growth factors; occurs in tissues incapable of cell division  
*Hyperplasia*: increased cell numbers in response to hormones and other growth factors; cells are able to divide  
*Atrophy*: decreased cell and organ size, as a result of decreased use or disuse; associated with decreased synthesis and increased proteolytic breakdown of organelles  
*Metaplasia*: change in phenotype of differentiated cells, often a replacement of one cell type by another that makes cells better able to withstand the stress; usually induced by alteration of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation.



## OVERVIEW OF CELL INJURY AND CELL DEATH



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 Figure 1-6 Cellular features of necrosis (*left*) and apoptosis (*right*). (Adapted from Walker NI, et al: Patterns of cell death. Methods Archiv Exp Pathol 13:18-32, 1988. With permission of S. Karger, Basel, Switzerland.)

**Table 1-1. Features of Necrosis and Apoptosis**

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

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page 7

As stated at the beginning of the chapter, cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Different injurious stimuli affect many metabolic pathways and cellular organelles. Injury may progress through a reversible stage and culminate in cell death (see Fig. 1-1).

*Reversible cell injury.* In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution. *Cell death.* With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. *There are two types of cell death-necrosis and apoptosis-which differ in their morphology, mechanisms, and roles in disease and physiology (Fig. 1-6 and Table 1-1).* When damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell, resulting in *necrosis*. Cellular contents also leak out through the damaged plasma membrane and elicit a host reaction (inflammation). Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma. When a cell is deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, the cell kills itself by another type of death, called *apoptosis*, which is characterized by nuclear dissolution without complete loss of membrane integrity. Apoptosis is an active, energy-dependent, tightly regulated type of cell death that is seen in some specific situations. *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury.* The morphologic features, mechanisms, and significance of these two death pathways are discussed in more detail later in the chapter.





## CAUSES OF CELL INJURY

The causes of cell injury range from the gross physical trauma of a motor vehicle accident to the single gene defect that results in a defective enzyme underlying a specific metabolic disease. Most injurious stimuli can be grouped into the following categories.

### *Oxygen Deprivation*

*Hypoxia*, or oxygen deficiency, interferes with aerobic oxidative respiration and is an extremely important and common cause of cell injury and death. Hypoxia should be distinguished from *ischemia*, which is a loss of blood supply in a tissue due to impeded arterial flow or reduced venous drainage. While ischemia is the most common cause of hypoxia, oxygen deficiency can also result from inadequate oxygenation of the blood, as in pneumonia, or reduction in the oxygen-carrying capacity of the blood, as in blood loss anemia or carbon monoxide (CO) poisoning. (CO forms a stable complex with hemoglobin that prevents oxygen binding.)

### *Chemical Agents*

An enormous number of chemical substances can injure cells; even innocuous substances such as [glucose](#) or salt, if sufficiently concentrated, can so derange the osmotic environment that cell injury or death results. Oxygen at sufficiently high partial pressures is also toxic. Agents commonly known as poisons cause severe damage at the cellular level by altering membrane permeability, osmotic homeostasis, or the integrity of an enzyme or cofactor, and exposure to these poisons can culminate in the death of the whole organism. Other potentially toxic agents are encountered daily in our environment; these include air pollutants, insecticides, CO, asbestos, and social "stimuli" such as ethanol. Even therapeutic drugs can cause cell or tissue injury in a susceptible patient or if used excessively or inappropriately ([Chapter 8](#)).

### *Infectious Agents*

These range from submicroscopic viruses to meter-long tapeworms; in between are the rickettsiae, bacteria, fungi, and protozoans. The diverse ways by which infectious pathogens cause injury are discussed in [Chapter 9](#).

### *Immunologic Reactions*

Although the immune system defends the body against pathogenic microbes, immune reactions can also result in cell and tissue injury. Examples include autoimmune reactions against one's own tissues and allergic reactions against environmental substances in genetically susceptible individuals ([Chapter 5](#)).

### *Genetic Defects*

Genetic defects can result in pathologic changes as conspicuous as the congenital malformations associated with Down syndrome or as subtle as the single amino acid substitution in hemoglobin S giving rise to sickle cell anemia. Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzymes in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair. Variations in the genetic makeup can also influence the susceptibility of cells to injury by chemicals and other environmental insults.

### *Nutritional Imbalances*

Even in the current era of burgeoning global affluence, nutritional deficiencies remain a major cause of cell injury. Protein-calorie insufficiency among undernourished populations is only the

cause of cell injury. Protein-calorie insufficiency among underprivileged populations is only the most obvious example; specific vitamin deficiencies are not uncommon even in developed countries with high standards of living ([Chapter 8](#)). Ironically, excesses of nutrition are also important causes of morbidity and mortality; for example, obesity markedly increases the risk for type 2 diabetes mellitus. Moreover, diets rich in animal fat are strongly implicated in the development of atherosclerosis as well as in increased vulnerability to many disorders, including cancer.

### *Physical Agents*

Trauma, extremes of temperatures, radiation, electric shock, and sudden changes in atmospheric pressure all have wide-ranging effects on cells ([Chapter 8](#)).

### *Aging*

Cellular senescence leads to alterations in replicative and repair abilities of individual cells and tissues. All of these changes result in a diminished ability to respond to damage and, eventually, the death of cells and of the organism. The mechanisms underlying cellular aging are discussed at the end of this chapter.







## THE MORPHOLOGY OF CELL AND TISSUE INJURY

It is useful to describe the basic alterations that occur in damaged cells before we discuss the biochemistry of these changes. All stresses and noxious influences exert their effects first at the molecular or biochemical level. *lost long before cell death occurs, and the morphologic changes of cell injury (or death) lag far behind.* For example, myocardial cells become noncontractile after 1 to 2 minutes of ischemia, although they do not die until several hours have elapsed. These myocytes do not appear dead by electron microscopy for 2 to 3 hours, and by light

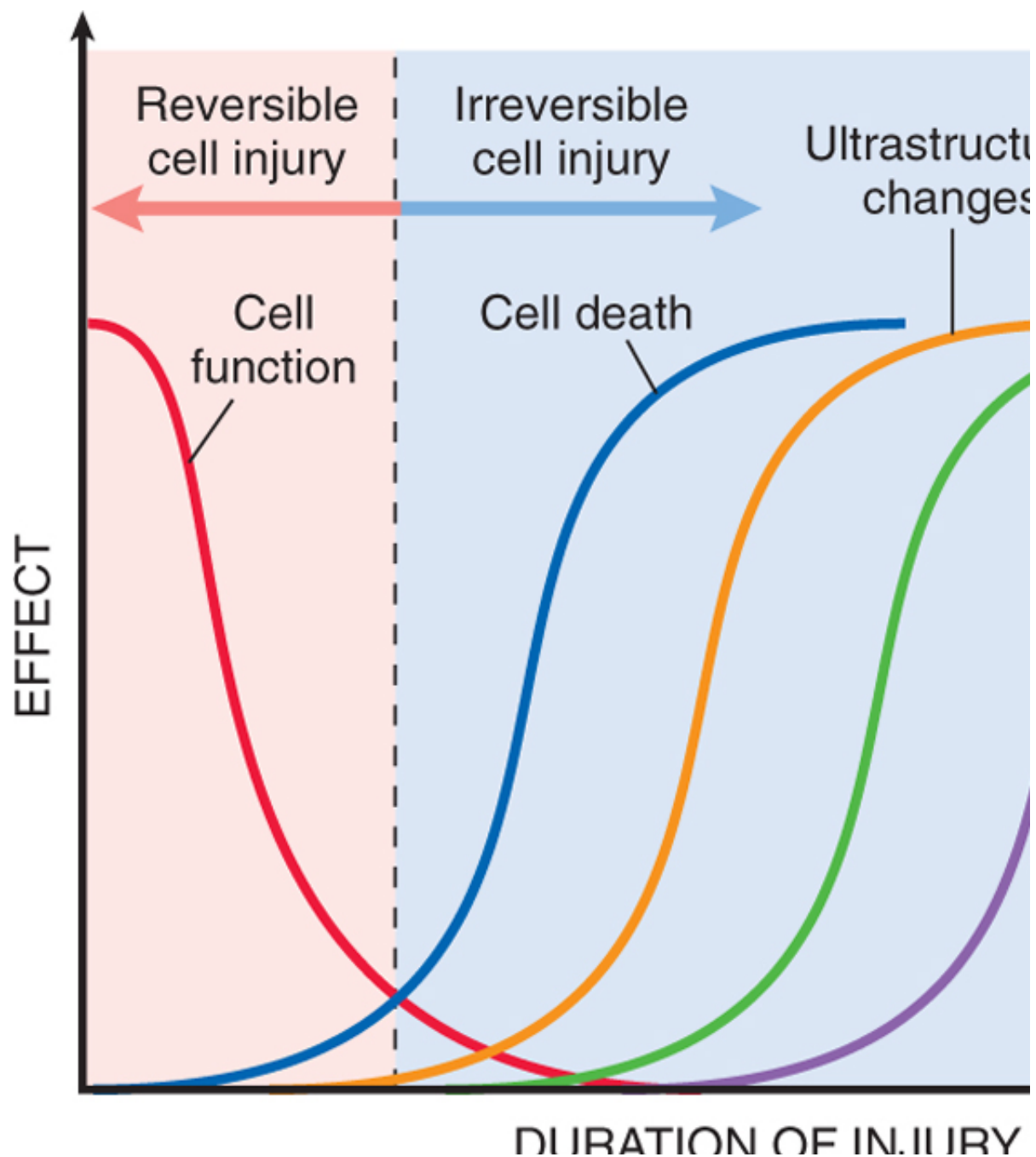


Figure 1-7 The relationship between cellular function, cell death, and the morphologic changes of cell injury. Note the onset of injury, although they are still viable, with potentially reversible damage; a longer duration of injury m death. Note also that cell death typically precedes ultrastructural, light microscopic, and grossly

The cellular derangements of reversible injury can be repaired and, if the injurious stimulus abates. Persistent or excessive injury, however, causes cells to pass the nebulous "point of no return" into events that determine when reversible injury becomes irreversible and progresses to cell death. The relevance of this question is obvious; if we can answer it we may be able to devise strategies for preventing permanent deleterious consequences. Although there are no definitive morphologic or biochemical *phenomena consistently characterize irreversibility: the inability to reverse mitochondrial dysfunction* (ATP generation) even after resolution of the original injury, and *profound disturbances in membrane* to lysosomal membranes results in the enzymatic dissolution of the injured cell that is characteristic

Different injurious stimuli may induce death by necrosis or apoptosis (see Fig. 1-6 and Table 1-1). Severe depletion of ATP and loss of membrane integrity are typically associated with necrosis. Apoptosis is a process not associated with ATP depletion and it has many unique features, which we will describe later.

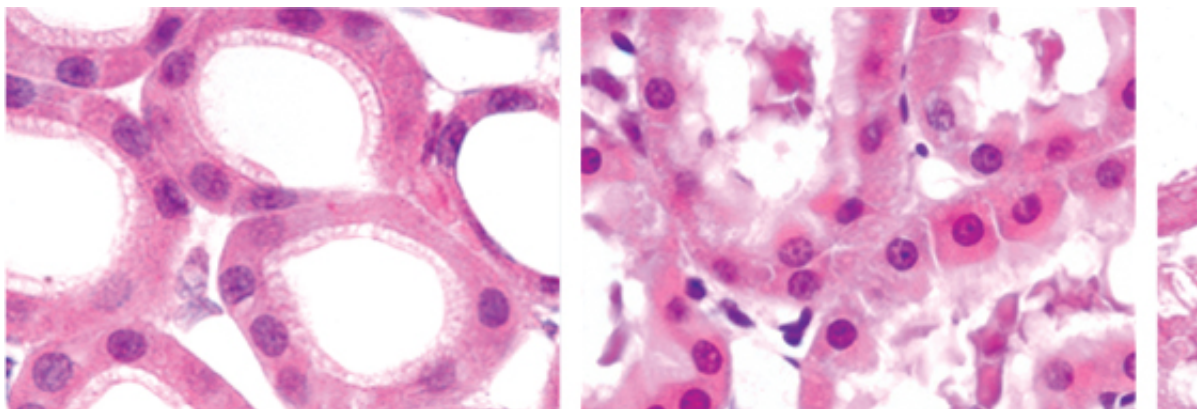
### Reversible Injury

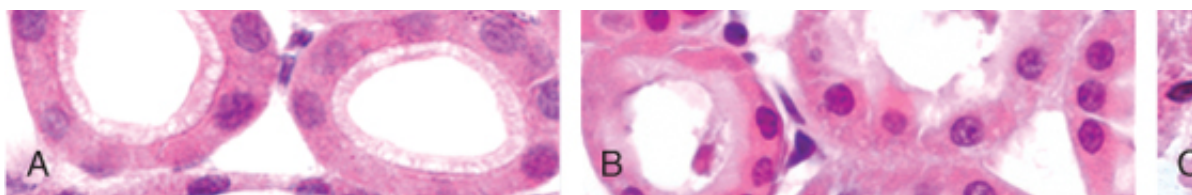
The two main morphologic correlates of reversible cell injury are *cellular swelling* and *fatty change*. Cellular swelling occurs in hypoxic injury and various forms of toxic or metabolic injury, and is manifested by the accumulation of fluid in the cytoplasm. It occurs mainly in cells involved in and dependent on fat metabolism, such as hepatocytes. The mechanisms of fatty change are discussed later in the chapter.

#### Morphology

**Cellular swelling** (Fig. 1-8B), the first manifestation of almost all forms of injury to appreciate with the light microscope; it may be more apparent at the level of the whole organ. In many cells in an organ it causes some pallor, increased turgor, and increase in weight. Microscopic examination may reveal small, clear vacuoles within the cytoplasm; thinning of the nucleus, and pinched-off segments of the ER. This pattern of nonlethal injury is sometimes called **vacuolar degeneration**. Swelling of cells is reversible. **Fatty change** is manifested by the presence of lipid vacuoles in the cytoplasm. It is principally encountered in cells participating in lipid metabolism (e.g., hepatocytes and myocardial cells) and is also reversible. Injured cells may also show increased eosinophilic staining, which becomes much more pronounced with progression to necrosis (described later).

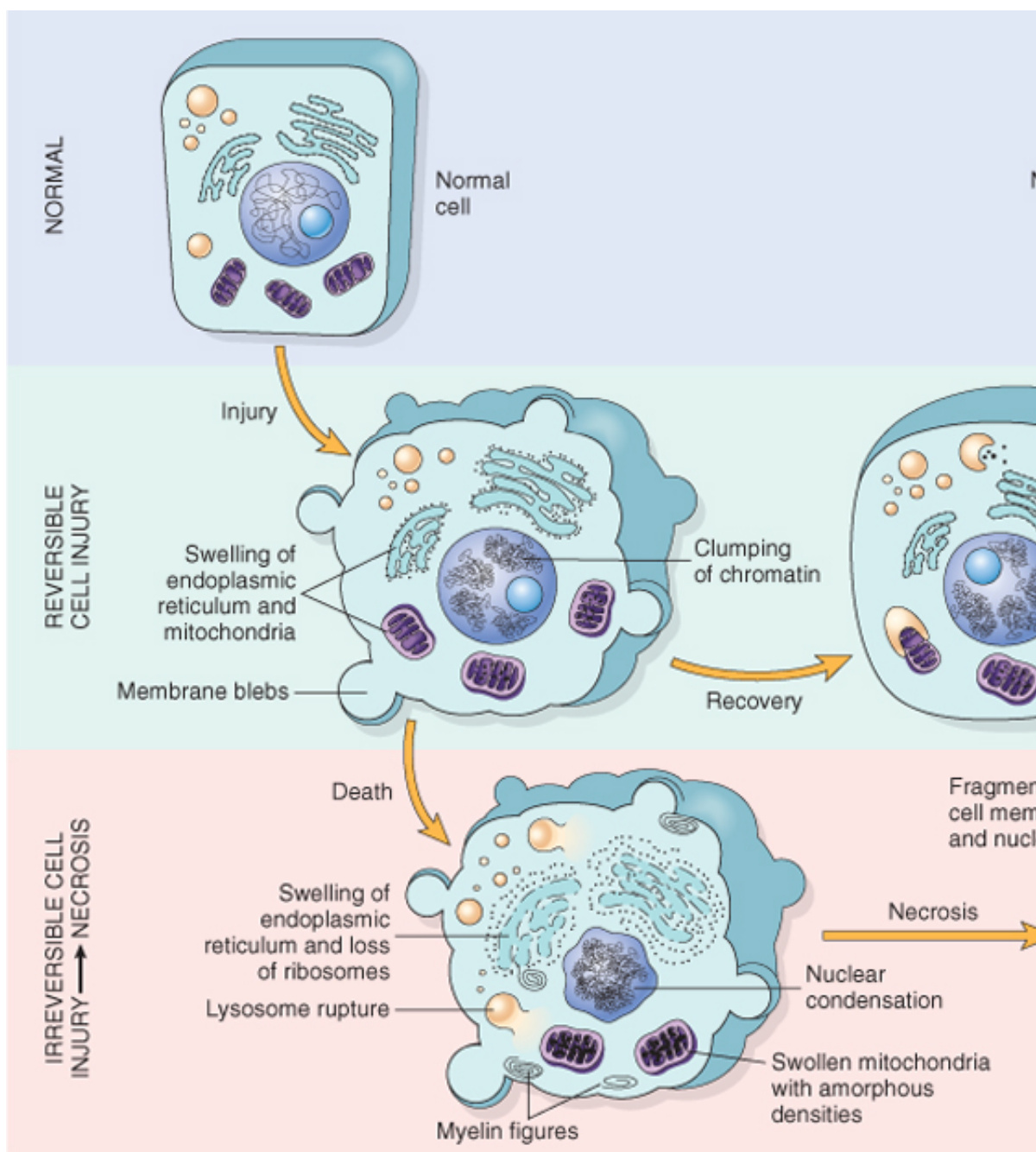
The ultrastructural changes of reversible cell injury are illustrated schematically in Figure 1-8A. The changes include: (1) plasma membrane alterations such as blebbing, blunting or distortion of microvilli, and detachment of intercellular attachments; (2) mitochondrial changes such as swelling and the appearance of amorphous densities; (3) dilation of the ER with detachment of ribosomes and (4) nuclear alterations, with clumping of chromatin.





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Figure 1-8 Morphologic changes in reversible and irreversible cell injury (necrosis). **A**, Normal kidney tubules with ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. **C**, No loss of nuclei and fragmentation of cells and leakage of contents. The ultrastructural features of these stages of cell injury are shown in the diagram below. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Cent



## Necrosis

The term *necrosis* was first used by morphologists to refer to a series of changes that accompany degradative action of enzymes on lethally injured cells. Necrotic cells are unable to maintain membranes and leak out. The enzymes responsible for digestion of the cell are derived either from the lysosomes of the cell or from lysosomes of leukocytes that are recruited as part of the inflammatory reaction to the dead cells.

### Morphology

In one common pattern of cell death resulting from lack of oxygen, the necrotic cell shows **eosinophilia** (i.e., pink staining from the eosin dye, the "E" in "H&E"). This is attributed to binding of eosin to denatured cytoplasmic proteins and in part to loss of the basophilic staining imparted by the ribonucleic acid (RNA) in the cytoplasm (basophilia is the blue staining imparted by the hematoxylin dye, the "H" in "H&E"). The cell may have a more glassy homogeneous appearance because of the loss of glycogen particles. When enzymes have digested the cytoplasm, the cytoplasm becomes vacuolated and appears moth-eaten. Dead cells may be replaced by phospholipid masses, called **myelin figures**, that are derived from damaged cellular membranes. They are thought to result from dissociation of lipoproteins with unmasking of phosphatide groups, followed by uptake and intercalation of water between the lamellar stacks of membranes. These precipitates are then either phagocytosed by other cells or further degraded into fatty acids. Such fatty acid residues result in the generation of calcium soaps. Thus, the dead cells may become **calcified**. By electron microscopy (see Fig. 1-9), necrotic cells are characterized by loss of plasma and organelle membranes, marked dilation of mitochondria with the appearance of membrane densities, disruption of lysosomes, intracytoplasmic myelin figures, and profound nuclear changes culminating in nuclear dissolution.

Nuclear changes assume one of three patterns, all due to breakdown of DNA and loss of the chromatin may fade (**karyolysis**), presumably secondary to deoxyribonuclease activity. A second pattern is **pyknosis**, characterized by nuclear shrinkage and increased basophilic staining as the chromatin condenses into a solid shrunken mass. In the third pattern, **karyorrhexis**, the pyknotic nucleus undergoes fragmentation. In 1 to 2 days, the nucleus in a dead cell completely disappears.

## SUMMARY

### Morphologic Alterations in Injured Cells

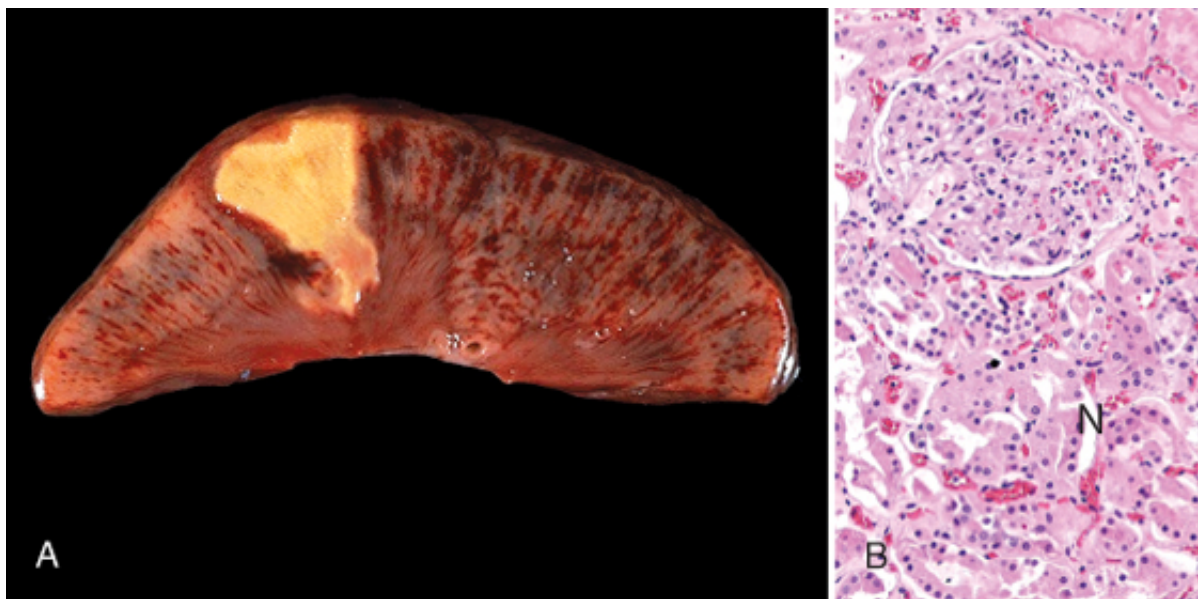
*Reversible cell injury:* cell swelling, fatty change, plasma membrane blebbing, mitochondrial swelling, dilation of the ER, eosinophilia (due to decreased cytoplasmic RNA); increased eosinophilia; nuclear shrinkage, fragmentation, and dissolution; breakdown of plasma membrane and organelle membranes; myelin figures; leakage and enzyme release of organelle contents. *Apoptosis:* nuclear chromatin condensation; formation of apoptotic bodies (shrunken nuclei and cytoplasm)

### Patterns of Tissue Necrosis

Necrosis of a collection of cells in a tissue or an organ, for instance in the ischemic myocardium, may involve sometimes an entire organ. There are several morphologically distinct patterns of tissue necrosis, depending on the underlying cause. Although the terms that describe these patterns do not reflect underlying mechanisms, their implications are understood by both pathologists and clinicians.







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 Figure 1-10 Coagulative necrosis. **A**, A wedge-shaped kidney infarct (yellow) with preservation of the outlines. **B**, normal kidney (N) and necrotic cells in the infarct (I). The necrotic cells show preserved outlines with loss of nuclei, to discern at this magnification).

### Morphology

**Coagulative necrosis** is a form of tissue necrosis in which the component cells and architecture is preserved for at least several days (Fig. 1-10). The affected tissues Presumably the injury denatures not only structural proteins but also enzymes and of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks. necrotic cells are removed by phagocytosis of the cellular debris by infiltrating leukocytes. the dead cells by the action of lysosomal enzymes of the leukocytes. Coagulative necrosis **infarcts** (areas of ischemic necrosis) in all solid organs except the brain.

**Liquefactive necrosis** is seen in focal bacterial or, occasionally, fungal infections, stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digests the dead tissue. For obscure reasons, hypoxic death of cells within the central nervous system often results in liquefactive necrosis (Fig. 1-11). Whatever the pathogenesis, liquefaction completely digests the dead tissue, transformation of the tissue into a liquid viscous mass. If the process was initiated by a bacterial infection, the material is frequently creamy yellow and is called **pus** (Chapter 2).

Although **gangrenous necrosis** is not a distinctive pattern of cell death, the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost blood supply and undergone coagulative necrosis involving multiple tissue layers. When bacterial infection is superimposed on coagulative necrosis is modified by the liquefactive action of the bacteria and the area is called **wet gangrene**.

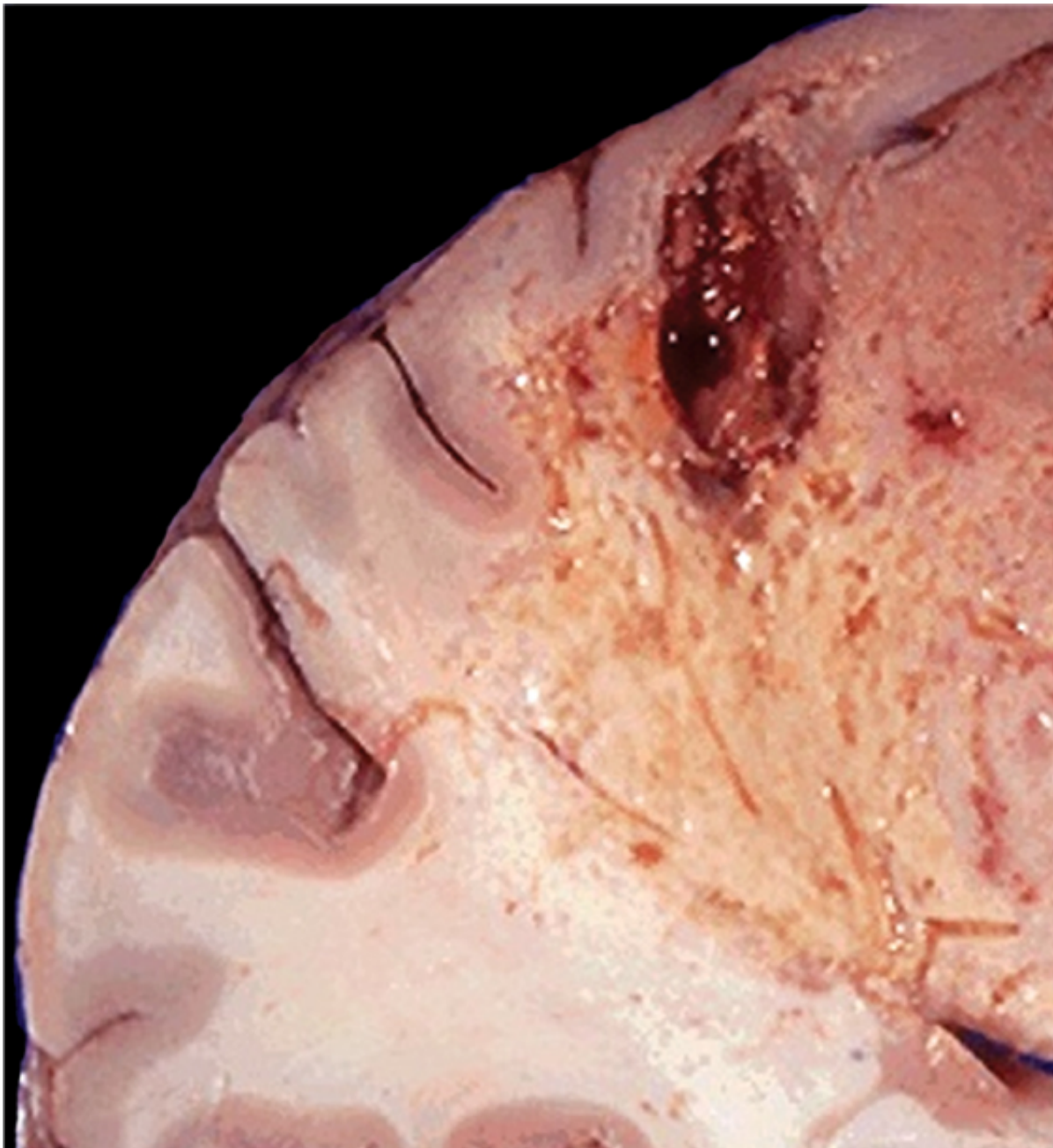
**Caseous necrosis** is encountered most often in foci of tuberculous infection. The appearance (Fig. 1-12) is derived from the friable yellow-white appearance of the area of necrosis (Fig. 1-12). On gross examination, the necrotic focus appears as a collection of fragmented or lysed cells with a granular appearance. Unlike coagulative necrosis, the tissue architecture is completely lost and cellular outlines cannot be discerned. Caseous necrosis is often enclosed within a border; this appearance is characteristic of a focus of inflammation known as a **granuloma**.

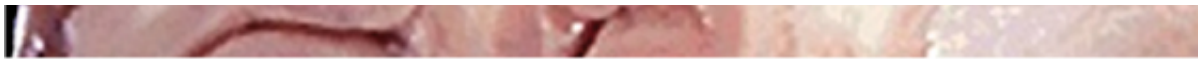
**Fat necrosis**, a term that is well fixed in medical parlance, refers to focal areas of necrosis of adipose tissue resulting from release of activated pancreatic lipases into the substance of the pancreas or into the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis.



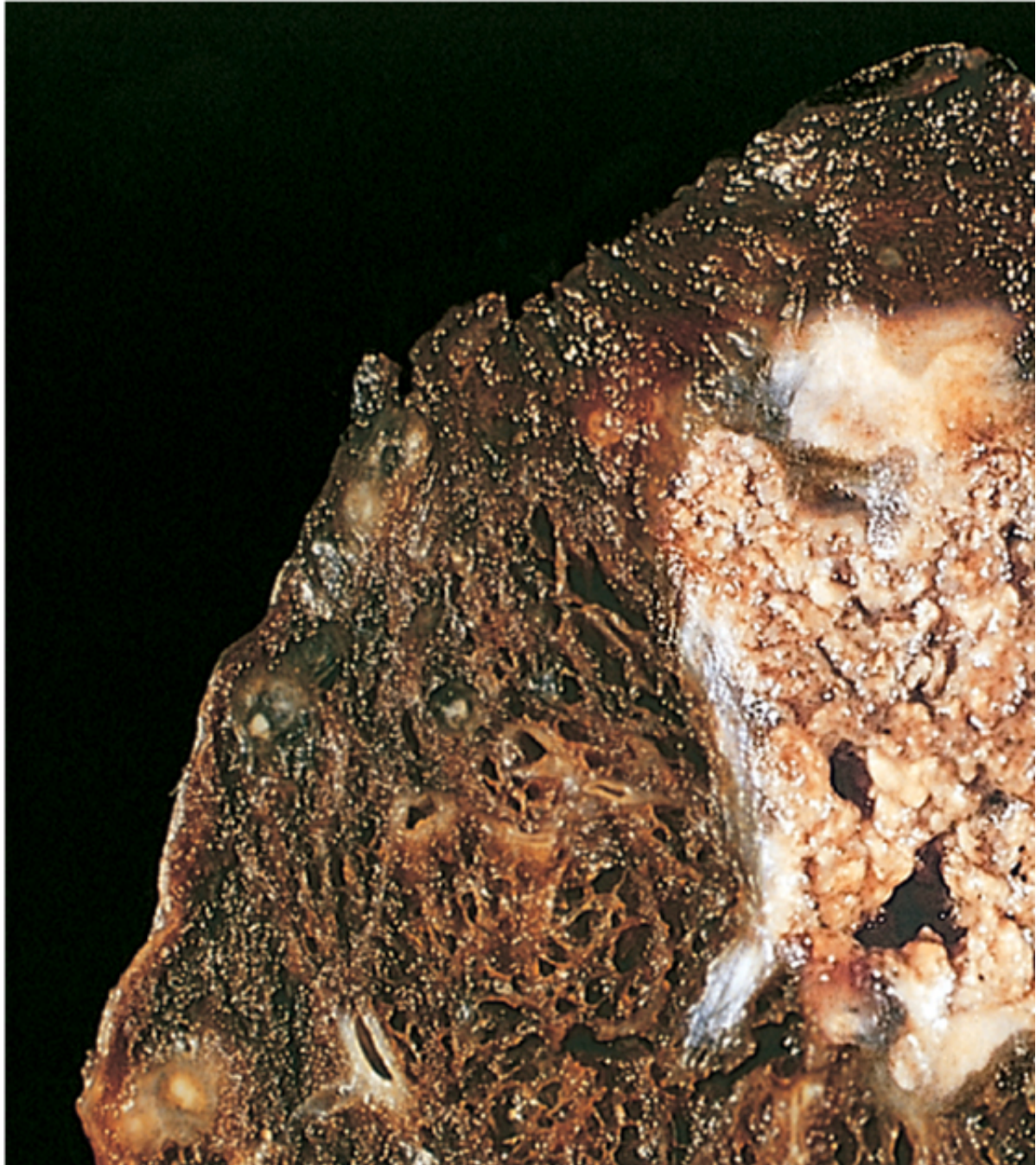
disorder, pancreatic enzymes that have leaked out of acinar cells and ducts liquefy cells in the peritoneum, and lipases split the triglyceride esters contained within fat acids combine with calcium to produce grossly visible chalky white areas (fat saponification) that help the surgeon and the pathologist to identify the lesions (Fig. 1-13). On histologic examination, these areas contain shadowy outlines of necrotic fat cells with basophilic calcium deposits and a surrounding inflammatory reaction.

**Fibrinoid necrosis** is a special form of necrosis usually seen in immune reactions. This pattern of necrosis is prominent when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes," together with fibrin that has leaked out of the vessels, give the area a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (Fig. 1-14). The immunologically mediated diseases (e.g., polyarteritis nodosa) in which this pattern of necrosis is seen are described in Chapter 5.





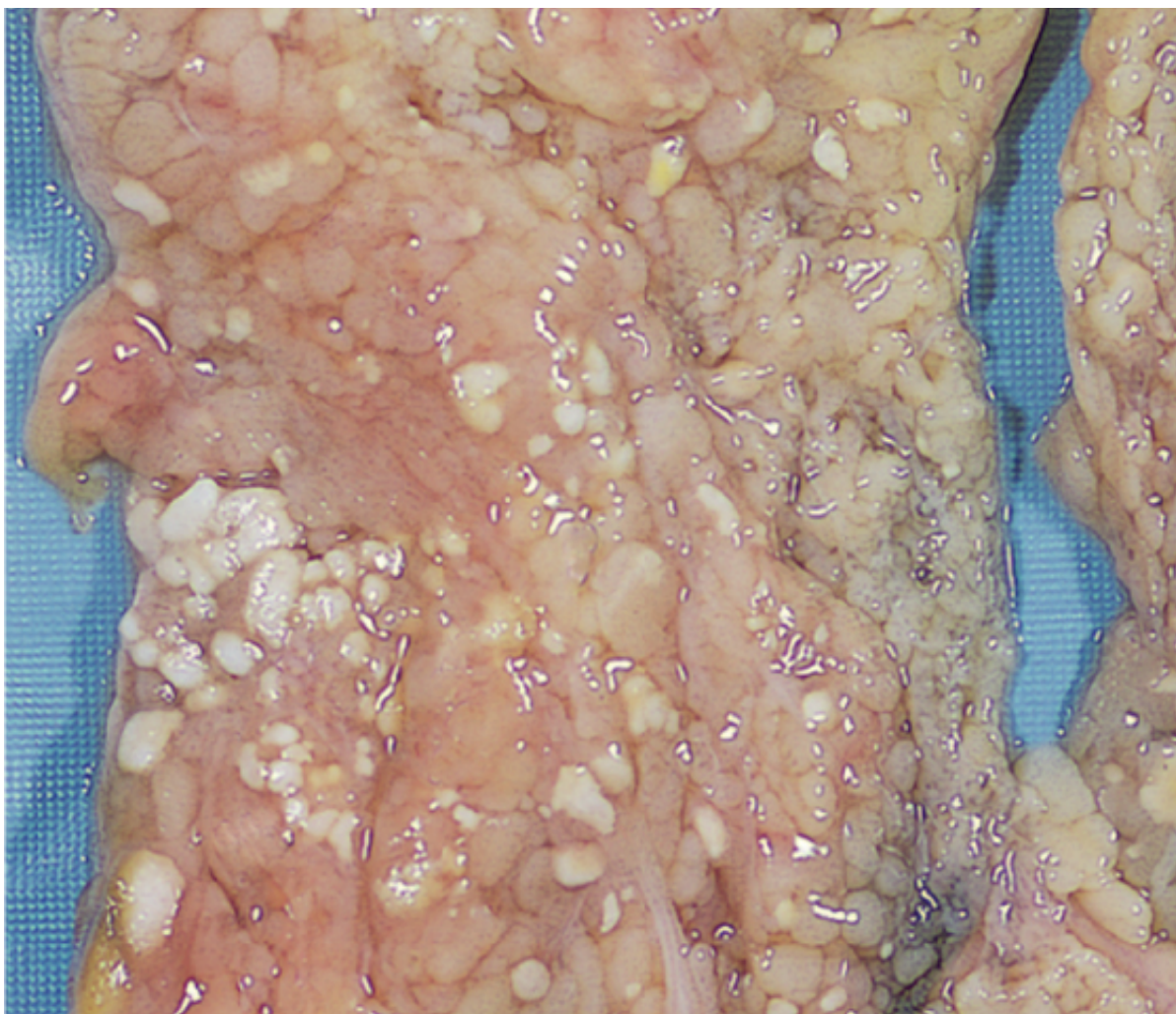
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Figure 1-11 Liquefactive necrosis. An infarct in the brain, showing dissolution of



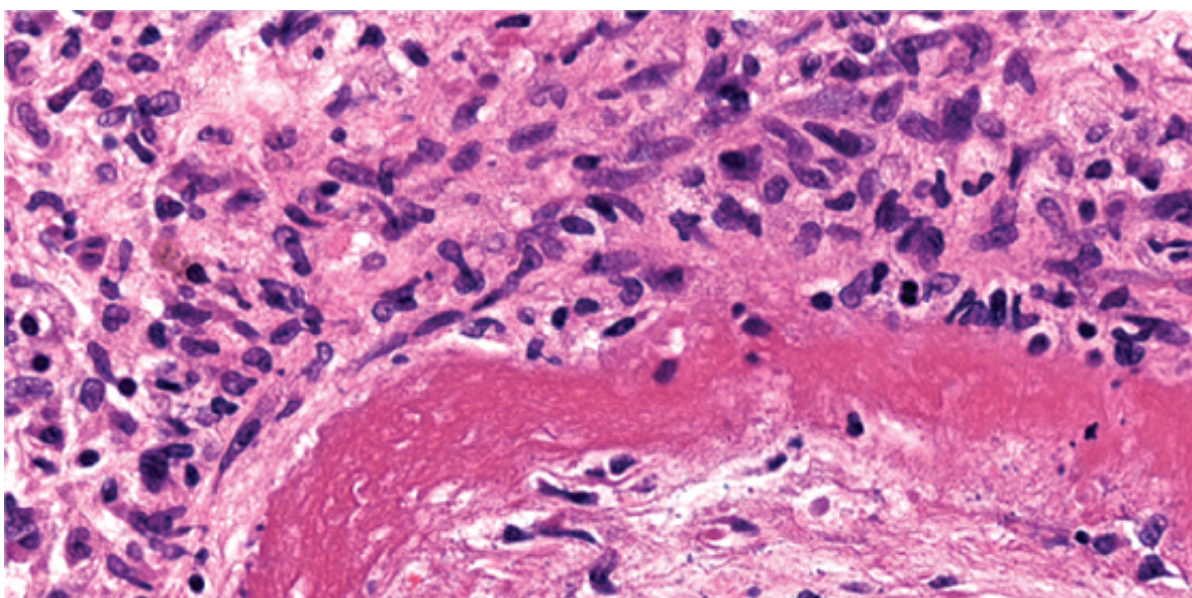
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Figure 1-12 Caseous necrosis. A tuberculous lung with a large area of caseous necrosis containing



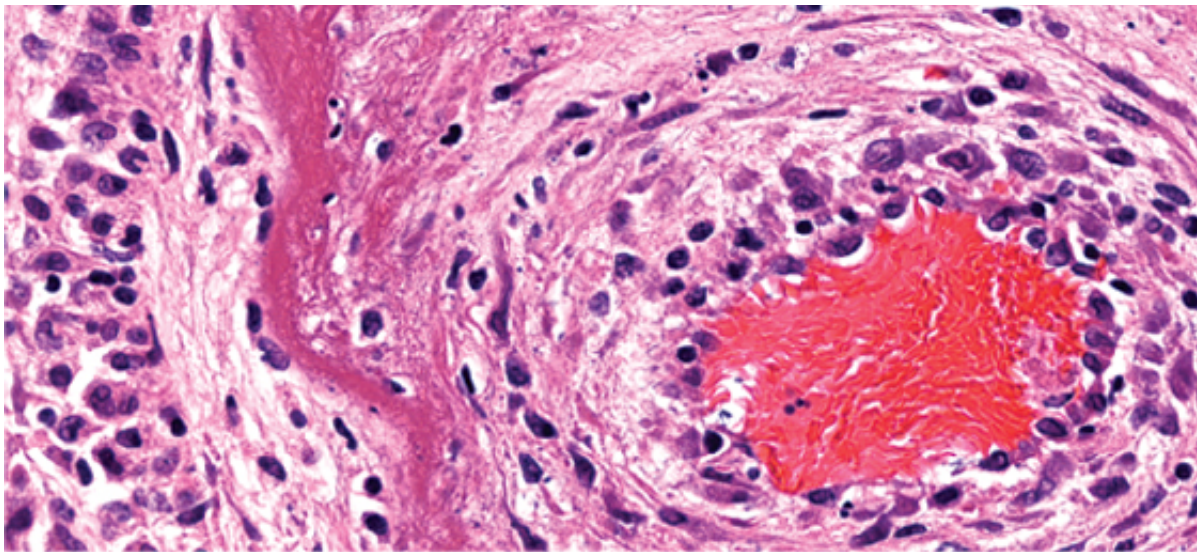




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Figure 1-13 Fat necrosis in acute pancreatitis. The areas of white chalky deposits represent foci of fat necrosis with  
of lipid breakdown in the mesentery.







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 Figure 1-14 Fibrinoid necrosis in an artery in a patient with polyarteritis nodosa. The wall of the artery shows a c protein deposition and inflammation (dark nuclei of neutrophils).

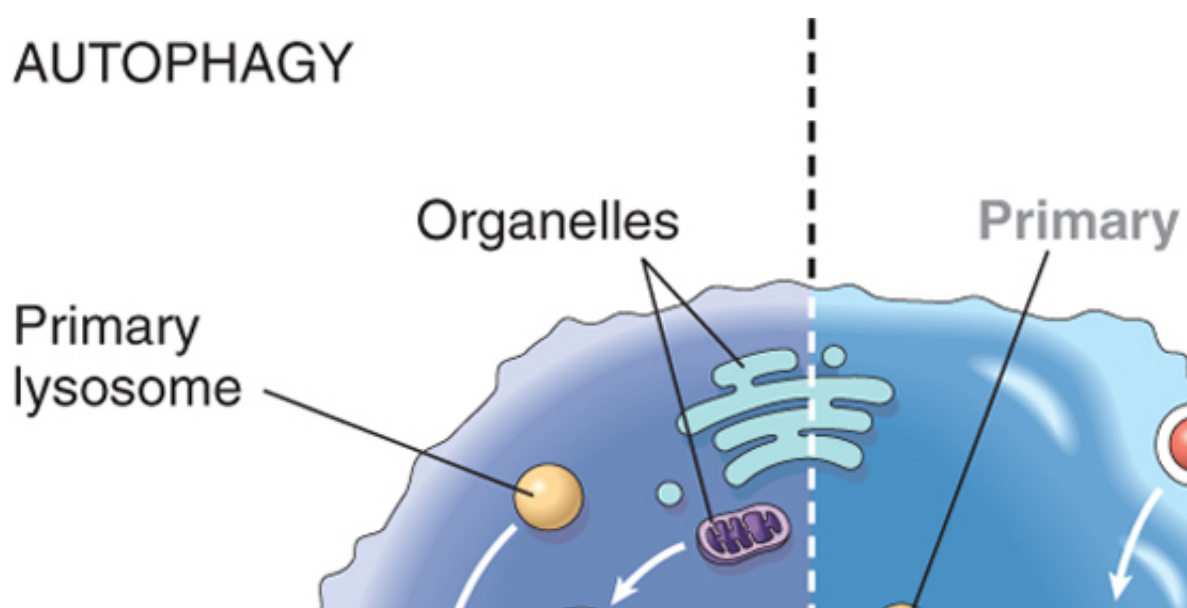
Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circ tissue-specific necrosis using blood or serum samples. Cardiac muscle, for example, contains a u kinase and of the contractile protein troponin, whereas hepatic bile duct epithelium contains a tem alkaline phosphatase, and hepatocytes contain transaminases. Irreversible injury and cell death ir serum levels of such proteins, and measurement of serum levels is used clinically to assess dama

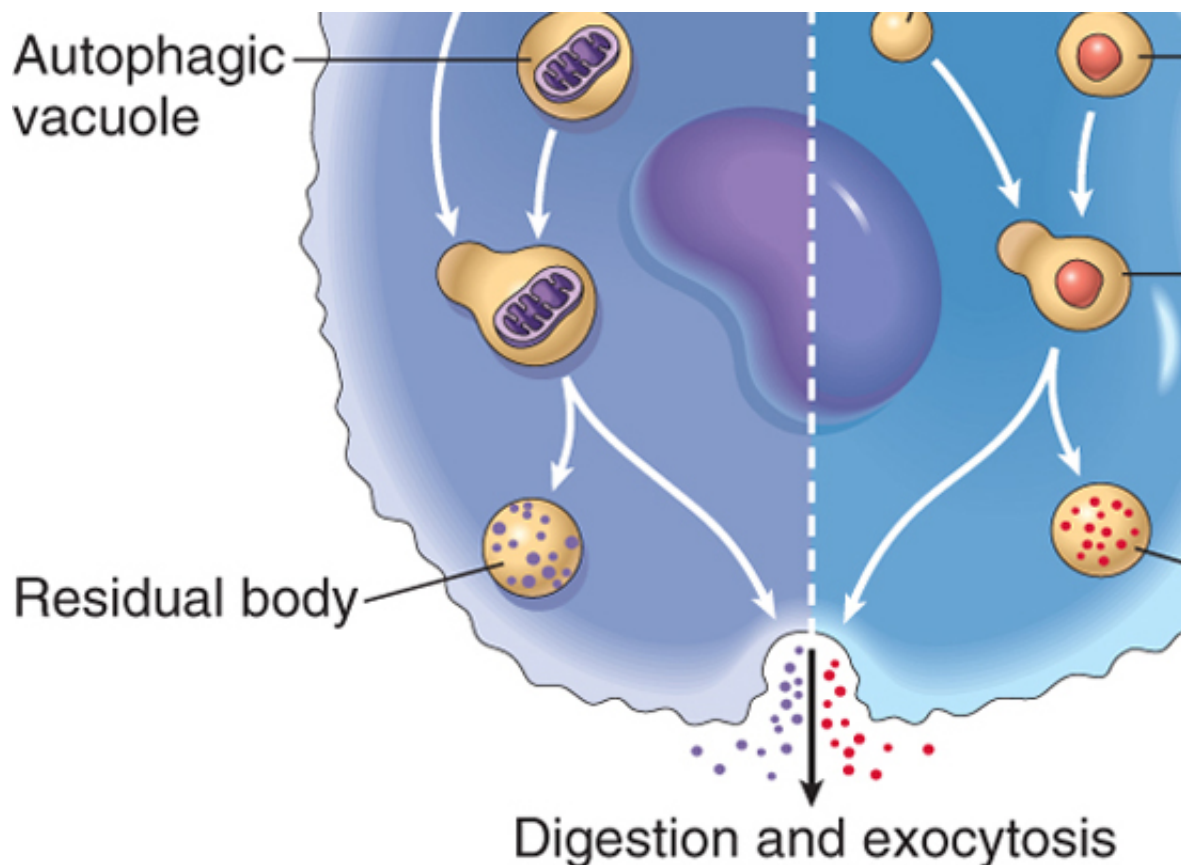
### Subcellular Responses to Injury

Thus far we have mainly focused on the whole tissue or the cell as a unit. However, certain agent alterations involving only subcellular organelles. Although some of these alterations occur in acute forms of cell injury, and still others are adaptive responses. In this section, some of the more com are discussed.

#### Autophagy

### AUTOPHAGY





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Figure 1-15 Autophagy (right) and heterophagy (left). (Redrawn from Fawcett DW: A Textbook of Histology, 11th

Autophagy refers to lysosomal digestion of the cell's own components and is contrasted with *heterophagy* (macrophage) ingests substances from the outside for intracellular destruction (Fig. 1-15). Autophagy occurs in times of nutrient deprivation, such that the starved cell lives by eating its own contents. In this process, portions of cytosol are first sequestered from the cytoplasm in an *autophagic vacuole* formed from rough endoplasmic reticulum (RER). The vacuole fuses with lysosomes to form an *autophagolysosome*, and the cellular components are digested by lysosomal enzymes. Autophagy is initiated by several proteins that sense nutrient deprivation. If it is not corrected, the cell may die by apoptosis, a way of telling a stressed or starved cell that it can no longer cope by living.

The enzymes in lysosomes can break down most proteins and carbohydrates, although some lipids are not digested. Undigested debris may persist within cells as *residual bodies* or may be extruded. *Lipofuscin pigment* is a brownish-yellow material resulting from free radical-mediated lipid peroxidation. Certain indigestible pigments, such as carbon, can persist in phagolysosomes of macrophages for years.

Lysosomes are also repositories wherein cells sequester materials that cannot be completely degraded. *Lysosomal storage disorders*, caused by deficiencies of enzymes that degrade various macromolecules, result in abnormal accumulation of metabolites in the lysosomes of cells all over the body; neurons are particularly susceptible to lethal consequences (Chapter 7).

#### Induction (Hypertrophy) of Smooth ER

The smooth ER (SER) is involved in the metabolism of various chemicals, and cells exposed to these chemicals undergo hypertrophy of the SER as an adaptive response that may have important functional consequences. For instance, barbiturates induce the cytochrome P-450 mixed-function oxidase system found in the SER. Prolonged use of barbiturates leads to a decrease in the effects of the drug and the need to use increasing doses. This adaptation is due to the hypertrophy of the SER of hepatocytes and increased P-450 enzymatic activity. Although P-450-mediated modification of many compounds are rendered *more* injurious by this process; one example is carbon tetrachloride, which is rendered more toxic by the P-450-mediated formation of a free radical.

products formed by this oxidative metabolism include reactive oxygen species (ROS), which can have increased capacity to metabolize other compounds handled by the same system. Thus, if patients increase their alcohol intake, they may have subtherapeutic levels of the antiseizure medication because of the alcohol.

### *Mitochondrial Alterations*

As described later, mitochondrial dysfunction plays an important role in acute cell injury and death; however, there may be alterations in the number, size, shape, and presumably function of mitochondria. In hypertrophy there is an increase in the number of mitochondria in cells; conversely, in mitochondrial atrophy (probably via autophagy). Mitochondria may assume extremely large and abnormal shapes in hepatocytes in various nutritional deficiencies and alcoholic liver disease. In certain inherited metabolic *mitochondrial myopathies*, defects in mitochondrial metabolism are associated with increased numbers of mitochondria containing abnormal cristae.

### *Cytoskeletal Abnormalities*

The cytoskeleton consists of actin and myosin filaments, microtubules, and various classes of intermediate filaments. Nonpolymerized and nonfilamentous forms of contractile proteins also contribute to the cellular structure. Many cellular functions, including

- Intracellular transport of organelles and molecules
- Maintenance of basic cell architecture (e.g., cell shape)
- Transmission of cell-cell and cell-extracellular matrix signals to the nucleus
- Maintenance of cell integrity
- Cell mobility
- Phagocytosis

Cells and tissues respond to environmental stresses (e.g., shear stress in blood vessels or increased pressure in the heart) by remodeling their intracellular scaffolding. Abnormalities of the cytoskeleton occur in a variety of pathologies and can be manifested as an abnormal appearance and function of cells (hypertrophic cardiomyopathy; [Cellular and Molecular Basis of Disease, 11e, Chapter 16](#)). Perturbations in the organization of *microtubules* can cause sterility by inhibiting sperm motility in the respiratory epithelium, resulting in chronic infections due to impaired clearance of inhaled bacteria (*Chronic Infection Syndrome*). Microtubules are also essential for leukocyte migration and phagocytosis. Drugs that inhibit microtubule polymerization (*colchicine*<sup>®</sup>) are useful in treating gout, in which symptoms are due to movement of macrophages to the site of inflammation. Since microtubules form the mitotic spindle, vinca alkaloids are also antiproliferative and may therefore be useful as antitumor agents.

## **SUMMARY**

### **Subcellular Alterations in Cell Injury: Effects of Injurious Agents on Organellar Components**

Some forms of cell injury affect particular organelles and have unique manifestations.

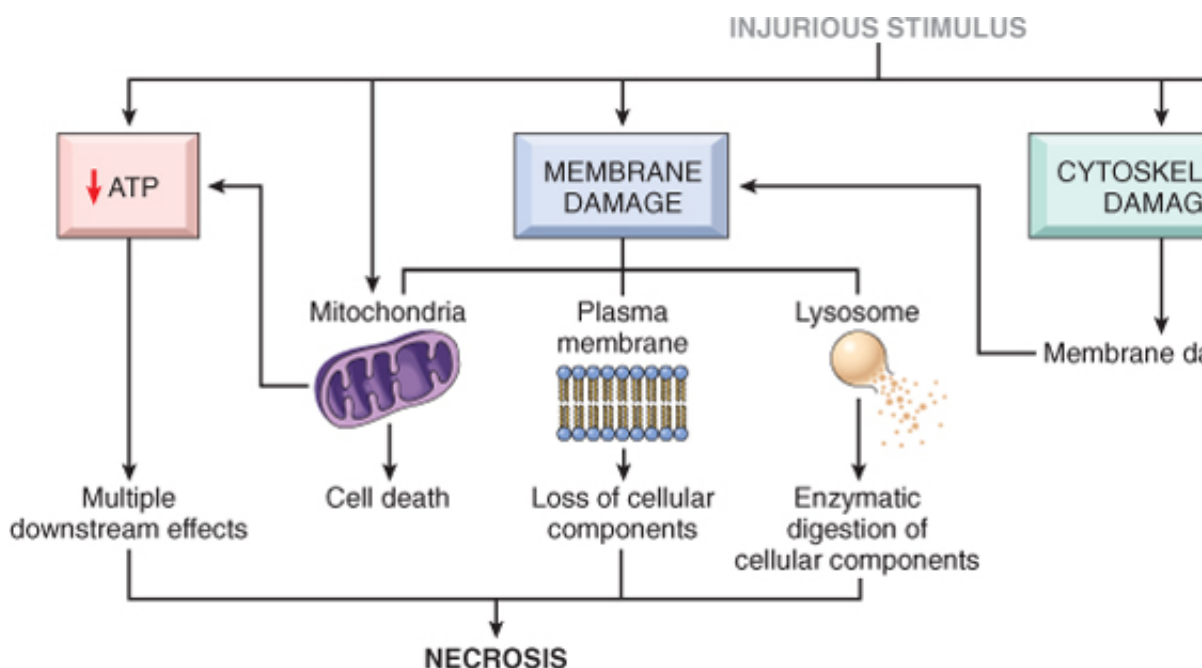
**Autophagy:** In nutrient-deprived cells, organelles are enclosed in vacuoles that are then digested. The organelles are digested but in some cases indigestible pigment (e.g., lipofuscin) remains. **Hypertrophy of SER:** Cells exposed to toxins that are metabolized in the ER undergo hypertrophy of the ER, a compensatory mechanism to maximize removal of toxins. **Mitochondrial alterations:** Changes in the number, size, and shape of mitochondria are seen in response to chronic injury. **Cytoskeletal alterations:** Some drugs and toxins affect the structure, assembly and functions of cytoskeletal filaments or result in abnormal accumulation of cytoskeletal components.



## MECHANISMS OF CELL INJURY

Now that we have discussed the causes of cell injury and necrosis and their morphologic and functional changes, we will discuss in more detail the molecular basis of cell injury, and then illustrate the important principles with a few examples of cell injury. The biochemical mechanisms linking any given injury with the resulting cellular and tissue changes are highly interconnected, and tightly interwoven with many intracellular metabolic pathways. It is therefore difficult to discuss the alterations caused by a particular insult. Nevertheless, several general principles are relevant to the understanding of cell injury.

*The cellular response to injurious stimuli depends on the type of injury, its duration, and its intensity. A brief duration of ischemia may lead to reversible cell injury, whereas larger toxin doses or longer durations of exposure lead to irreversible injury and cell death. The consequences of an injurious stimulus depend on the nature of the stimulus and the makeup of the injured cell.* The same injury has vastly different outcomes depending on the nature of the stimulus and the makeup of the injured cell. For instance, a leg that is immobilized in the leg accommodates complete ischemia for 2 to 3 hours without irreversible injury, whereas a leg that is immobilized for 30 minutes. The nutritional (or hormonal) status can also be important; clearly, a glycogen-rich cell is much better than one that has just burned its last glucose<sup>Rx</sup> molecule. Genetic determinants of cellular response also be important. For instance, when exposed to the same dose of a toxin, individuals who have different levels of cytochrome P-450 may catabolize the toxin at different rates, leading to different outcomes. The study of the role of genetic polymorphisms in responses to drugs and toxins and in drug-drug interactions is called pharmacogenomics. *Cell injury results from functional and biochemical damage to essential cellular components (Fig. 1-16).* The most important targets of injurious stimuli are (1) the generation; (2) cell membranes, on which the ionic and osmotic homeostasis of the cell depends; (3) protein synthesis; (4) the cytoskeleton; and (5) the genetic apparatus of the cell.



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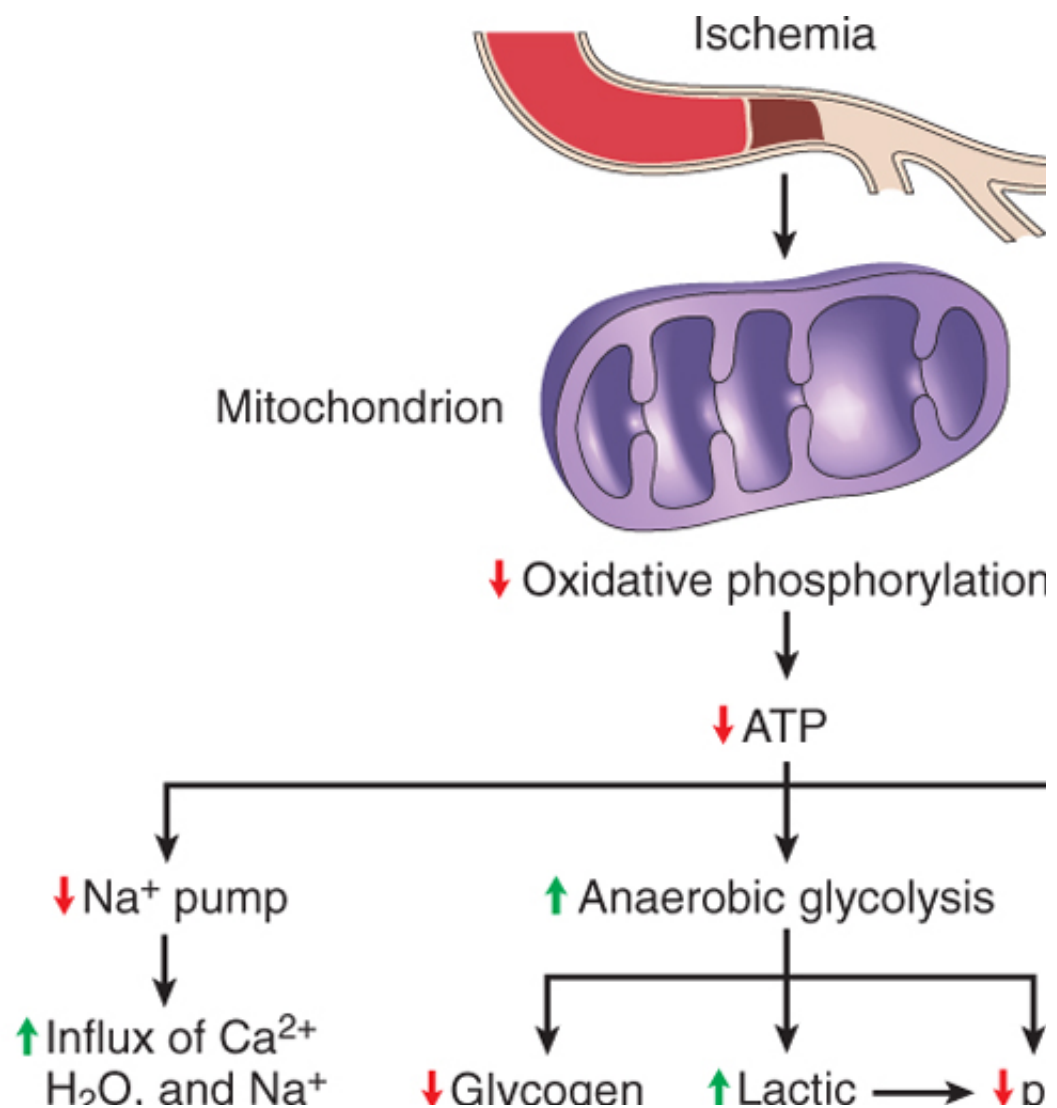
Figure 1-16 The principal cellular and biochemical sites of damage in cell injury. Note that loss of adenosine<sup>Rx</sup> triphosphate (shown) and culminates in necrosis. Mitochondrial damage may lead to reversible injury and de

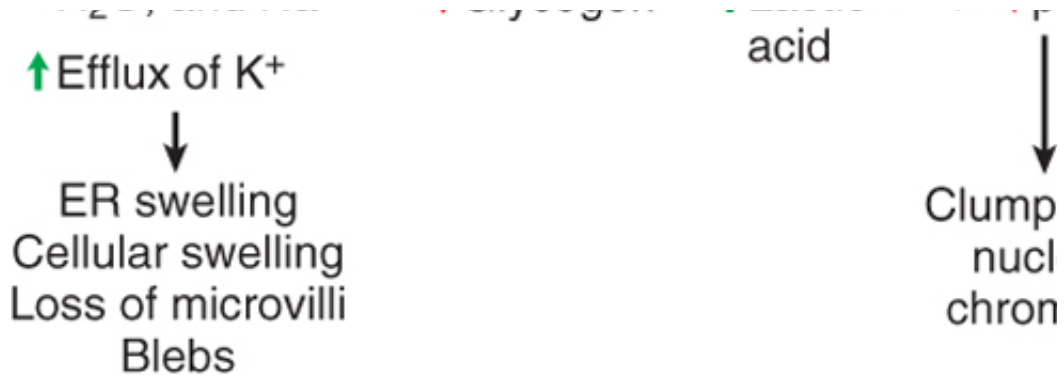
### Depletion of ATP



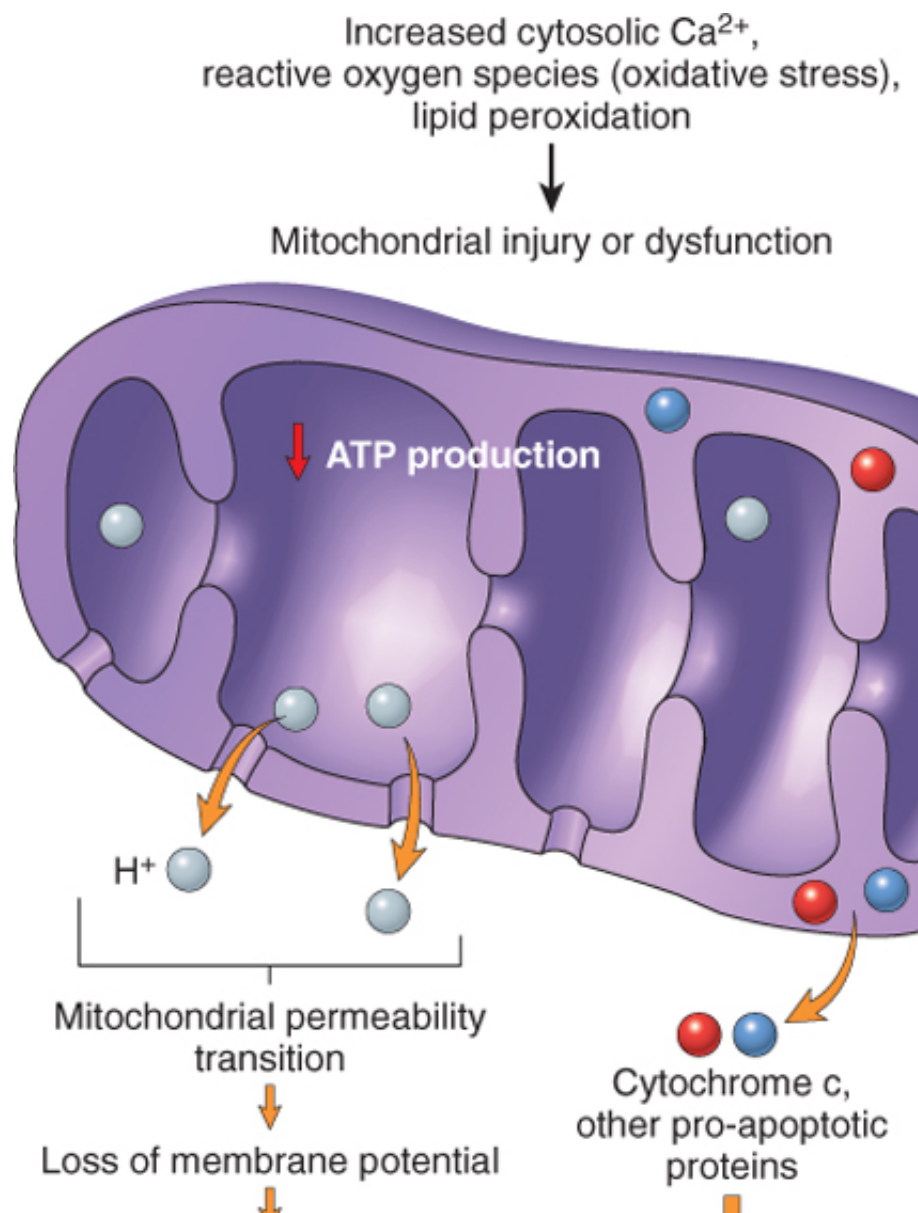
ATP, the energy store of cells, is produced mainly by oxidative phosphorylation of **adenosine**<sup>®</sup> diphosphate in the electron transport system of mitochondria. In addition, the glycolytic pathway can generate ATP using **glucose**<sup>®</sup> derived either from the circulation or from the hydrolysis of intracellular glycogen. Cells with a reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e.g., cyanide) are unable to survive loss of oxygen and decreased oxidative phosphorylation. Cells with a limited capacity for glycolysis (e.g., the brain) are unable to survive loss of oxygen and decreased oxidative phosphorylation. High-energy phosphate in the form of ATP is required for many degradative processes within the cell, including membrane transport, protein synthesis, lipogenesis, and other reactions necessary for phospholipid turnover. *Depletion of ATP to less than 5% to 10% of normal leads to failure of critical cellular systems (Fig. 1-17).*

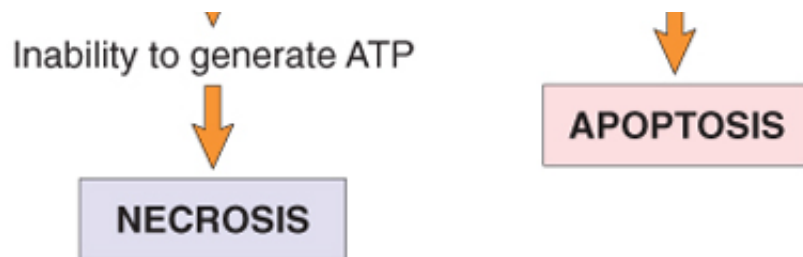
The activity of the *plasma membrane energy-dependent sodium pump* is reduced, resulting in a net gain of solute and efflux of potassium. The net gain of solute is accompanied by iso-osmotic gain of water. There is a compensatory *increase in anaerobic glycolysis* in an attempt to maintain ATP production. As a consequence, intracellular glycogen stores are rapidly depleted, and **lactic acid**<sup>®</sup> accumulates, leading to decreased activity of many cellular enzymes. *Failure of the  $\text{Ca}^{2+}$  pump* leads to influx of calcium and numerous cellular components, described below. Prolonged or worsening depletion of ATP leads to failure of the *protein synthetic apparatus*, manifested as detachment of ribosomes from the rough endoplasmic reticulum, with polysomes into monosomes, with a consequent reduction in protein synthesis. Ultimately, the cell undergoes necrosis.





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Figure 1-17 The initial functional and morphologic consequences of decreased intracellular adenosine<sub>3</sub> triphosph  
reticulum.





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Figure 1-18 Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apopt

### Damage to Mitochondria

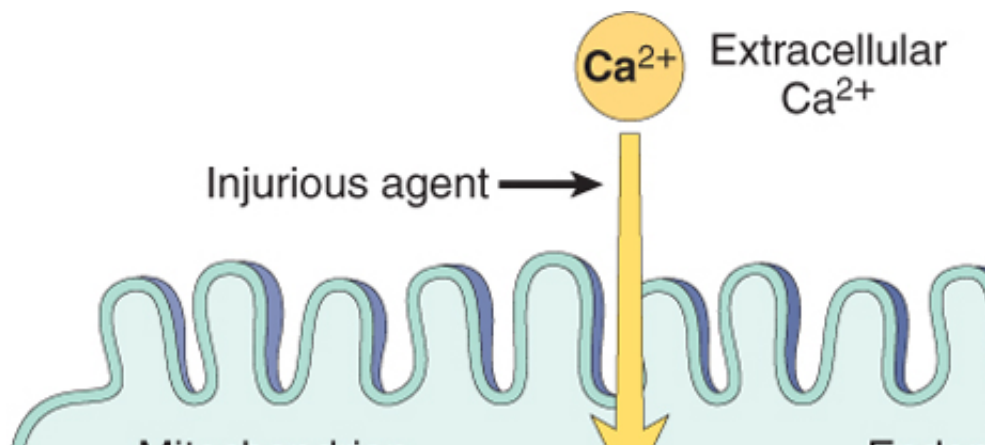
Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also Mitochondria can be damaged by increases of cytosolic  $\text{Ca}^{2+}$ , reactive oxygen species (discussed later). They are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins. There are several types of damage (Fig. 1-18):

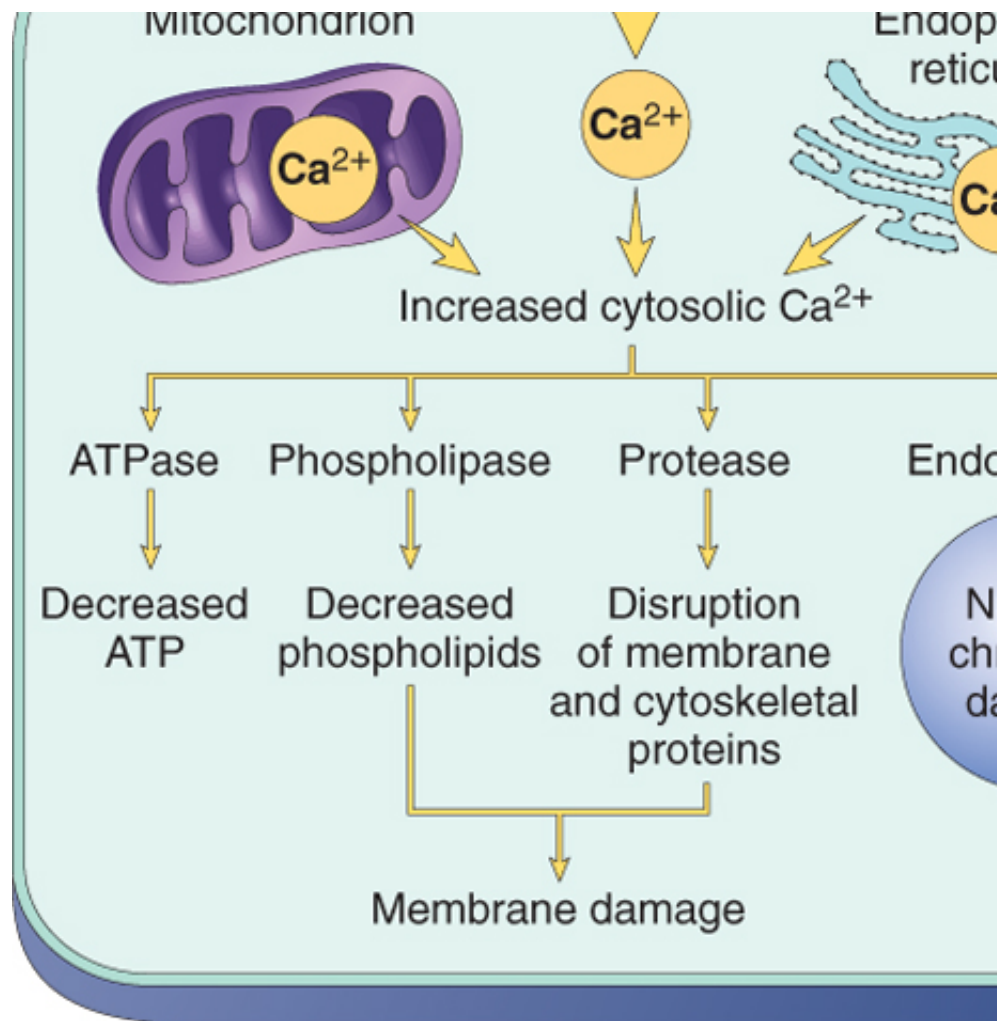
Mitochondrial damage often results in the formation of a high-conductance channel in the mitochondrial membrane, the permeability transition pore. The opening of this channel leads to the loss of  $\text{pH}$  changes, resulting in *failure of oxidative phosphorylation and progressive depletion of ATP*. The mitochondria also contain several proteins that are capable of activating apoptotic pathways (e.g., cytochrome *c*, a major protein involved in electron transport). Increased permeability of the mitochondrial membrane allows proteins to leak into the cytosol and *death by apoptosis*. Thus, cytochrome *c* plays a key dual role: its normal location inside mitochondria, it is essential for energy generation and the life of the cell, but severely that cytochrome *c* leaks out, it signals cells to die.

### Influx of Calcium

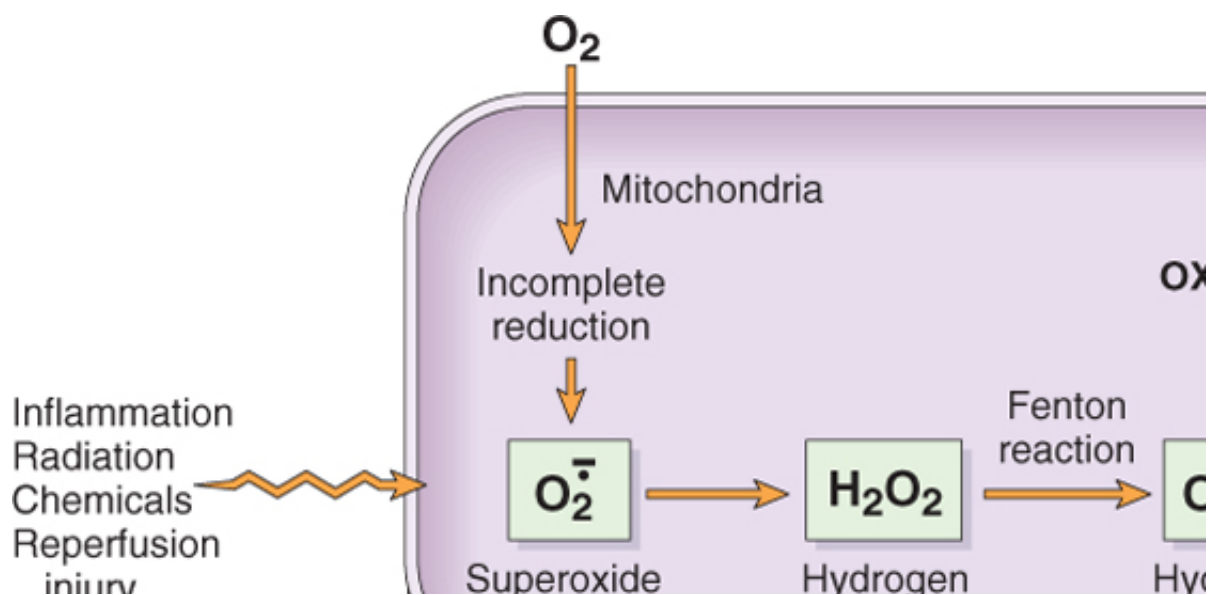
Cytosolic free calcium is normally maintained by ATP-dependent calcium transporters at concentrations lower than the concentration of extracellular calcium or of sequestered intracellular mitochondrial calcium. Injurious agents cause an increase in cytosolic calcium concentration, initially because of release of  $\text{Ca}^{2+}$  from intracellular stores, resulting from increased influx across the plasma membrane. *Increased cytosolic  $\text{Ca}^{2+}$  activates a number of deleterious cellular effects (Fig. 1-19)*. These enzymes include phospholipases (which cause membrane damage), endonucleases (which are responsible for DNA damage), and adenosine triphosphatases (ATPases; thereby hastening ATP depletion). Increased intracellular calcium leads to apoptosis, by direct activation of caspases and by increasing mitochondrial permeability. The importance of calcium is established by the finding that depleting extracellular  $\text{Ca}^{2+}$  delays cell death after hypoxia and exposure to toxins.

### Accumulation of Oxygen-Derived Free Radicals (Oxidative Stress)

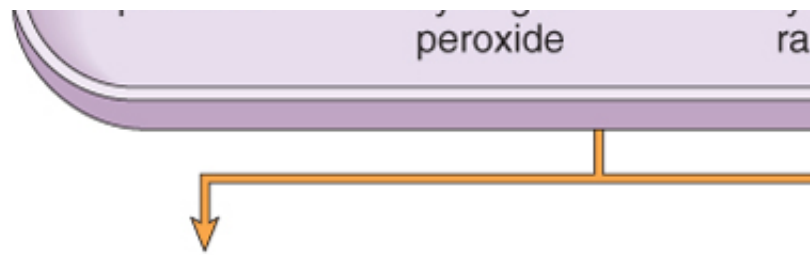




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Figure 1-19 Sources and consequences of increased cytosolic calcium in cell injury. ATP, Adenosine triphosphate.



injury



## PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH

ROS react with:

- Fatty acids  $\rightarrow$  oxidation  $\rightarrow$  generation of lipid peroxidases  $\rightarrow$  disruption of plasma membrane, organelles
- Proteins  $\rightarrow$  oxidation  $\rightarrow$  loss of enzymatic activity, abnormal folding
- DNA  $\rightarrow$  oxidation  $\rightarrow$  mutations, breaks

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Figure 1-20 The role of reactive oxygen species (ROS) in cell injury.  $O_2$  is converted

$O_2^{\cdot -}$  by oxidative enzymes in the endoplasmic reticulum, mitochondria, plasma membrane,  $O_2^{\cdot -}$  is converted to  $H_2O_2$  by dismutation and thence to  $OH^{\cdot}$  by the  $Cu^{2+}/Fe^{2+}$ -catalyzed Fenton reaction.  $H_2O_2$  peroxisomes (not shown). Also not shown is another potentially injurious free radical, singlet oxygen. Resultant proteins, and deoxyribonucleic acid (DNA) leads to various forms of cell injury. The major antioxidant enzymes are glutathione peroxidase.

Free radicals are chemical species with a single unpaired electron in an outer orbital. Such chemicals readily react with inorganic and organic chemicals; when generated in cells they avidly attack nucleic acids, proteins, and lipids. In addition, free radicals initiate autocatalytic reactions; molecules that react with free radicals, thus propagating the chain of damage. *Reactive oxygen species (ROS)* are a type of free radical. Cell injury by free radicals is well established. They are produced normally in cells during mitochondrial respiration and are degraded and removed by cellular defense systems. When the production of ROS increases or the removal is impaired, the result is an excess of these free radicals, leading to a condition called *oxidative stress*. Cell injury by free radicals; these situations include ischemia-reperfusion (discussed below), chemical and radiation injury, and other gases, cellular aging, microbial killing by phagocytic cells, and tissue injury caused by inflammation.

The accumulation of free radicals is determined by their rates of production and removal (Fig. 1-20). The *generation of free radicals*.

The reduction-oxidation (redox) reactions that occur during normal mitochondrial metabolism. For example, molecular oxygen is sequentially reduced in mitochondria by the addition of four electrons. In this process, small amounts of toxic intermediate species are generated by partial reduction of oxygen: superoxide ( $O_2^{\cdot -}$ ), hydrogen peroxide ( $H_2O_2$ ), and  $OH^{\cdot}$ .

Transition metals such as copper and iron also catalyze certain intracellular reactions and thereby catalyze free-radical formation, as in the Fenton reaction ( $OH^{\cdot} = H_2O_2 + Fe^{2+} \rightarrow OH_2 + Fe^{3+}$ ). The absorption of radiant energy (e.g., ultraviolet light, x-rays). Ionizing radiation generates free radicals (e.g.,  $H^{\cdot}$ ). The enzymatic metabolism of exogenous chemicals (e.g., drugs) also generates free radicals.



and hydrogen (H<sup>+</sup>) free radicals. The enzymatic metabolism of exogenous chemicals (e.g., later) Inflammation, because free radicals are produced by leukocytes that enter tissues (see important chemical mediator normally synthesized by a variety of cell types (Chapter 2), can be converted into highly reactive nitrite species

Cells have developed many *mechanisms to remove free radicals* and thereby minimize injury. Free radicals decay spontaneously. There are also several nonenzymatic and enzymatic systems that contribute to their removal (see Fig. 1-20).

The rate of spontaneous decay of superoxide is significantly increased by the action of superoxide dismutase (SOD) in many cell types (catalyzing the reaction

$2\text{O}_2^{\cdot -} + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$ ). Glutathione (GSH) peroxidase also protects against injury by catalyzing the reaction

$2\text{OH}^{\cdot -} + 2\text{GSH} \rightarrow 2\text{H}_2\text{O} + \text{GSSG}$  (glutathione homodimer). The intracellular ratio of oxidized to reduced glutathione (GSH) is a reflection of the oxidative state of the cell and an important aspect of cellular redox balance.

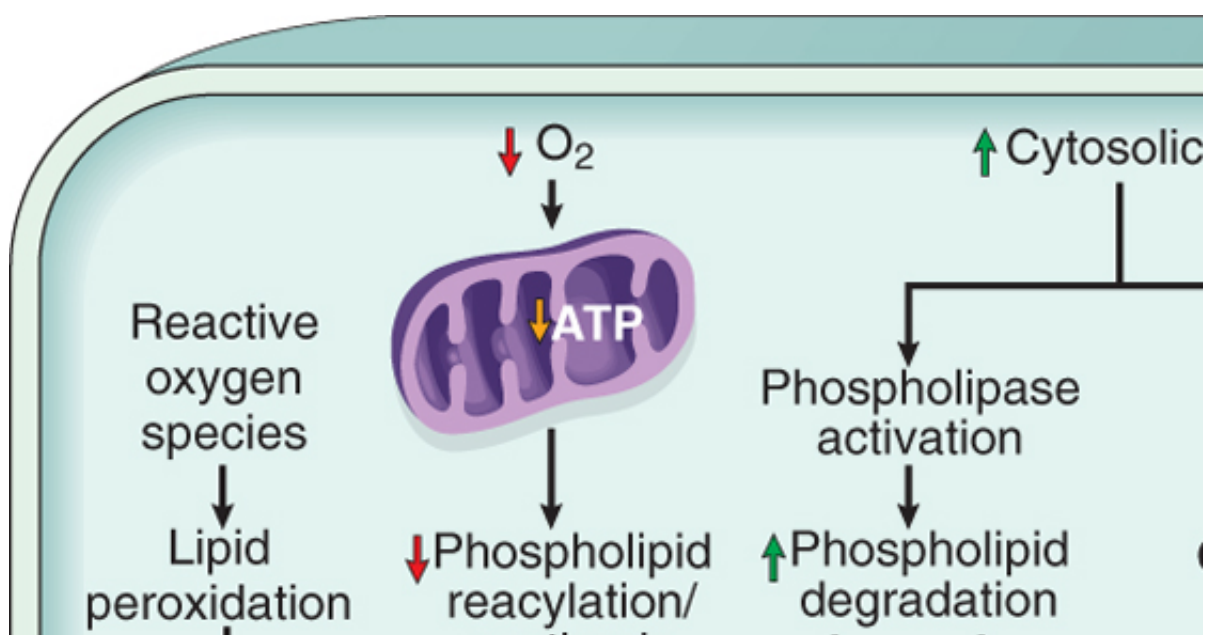
Catalase, present in peroxisomes, directs the degradation of hydrogen peroxide ( $2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$ ). Several exogenous antioxidants (e.g., vitamins E, A, and C, and  $\beta$ -carotene) may either block the formation of free radicals or neutralize them once they have formed.

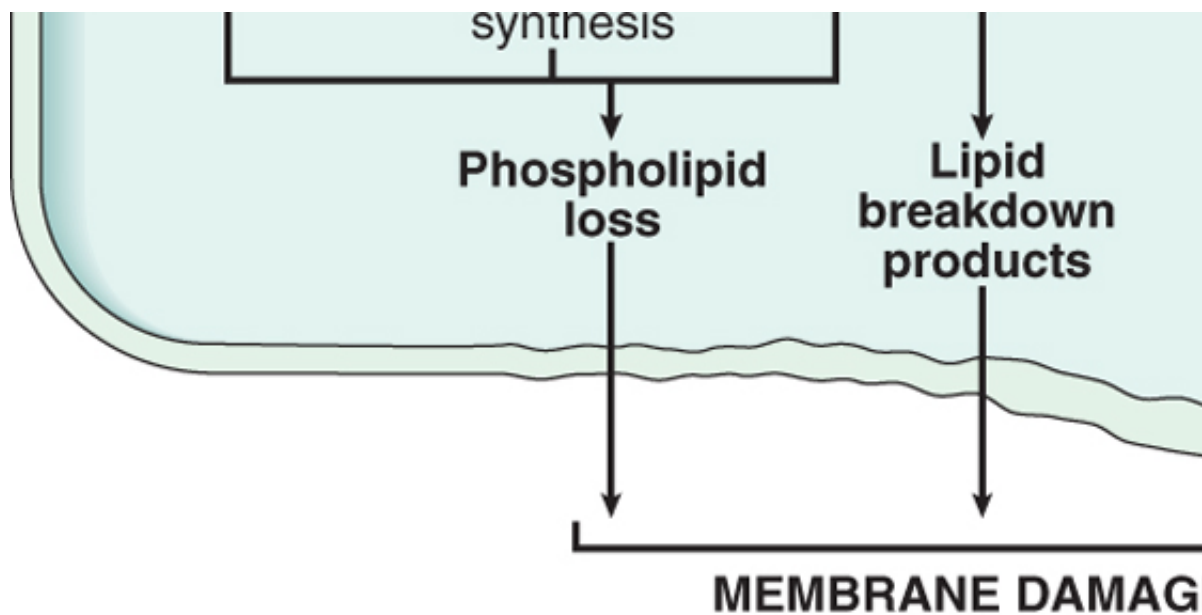
As mentioned above, *iron* and *copper* can catalyze the formation of free radicals. These metals are reduced by binding of the ions to storage and transport proteins (e.g., transferrin and ceruloplasmin), thereby decreasing the formation of ROS.

ROS have many diverse effects on cells and have even been implicated in activation of cells by a variety of stimuli. Three reactions are particularly relevant to *cell injury mediated by free radicals* (see Fig. 1-20):

**Lipid peroxidation of membranes.** Double bonds in membrane polyunsaturated lipids are vulnerable to attack by free radicals. The lipid-radical interactions yield peroxides, which are themselves unstable and can undergo further reactions, leading to cell injury. **Cross-linking of proteins.** Free radicals promote sulfhydryl-mediated protein cross-linking, leading to protein aggregation, degradation or loss of enzymatic activity. Free-radical reactions may also directly cause protein cross-linking. **DNA fragmentation.** Free-radical reactions with thymine in nuclear and mitochondrial DNA produce thymine radicals, leading to DNA fragmentation. DNA damage has been implicated in cell death, aging, and malignant transformation of cells.

## Defects in Membrane Permeability





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Figure 1-21 Mechanisms of membrane damage in cell injury. Decreased  $O_2$  and increased cytosolic  $Ca^{2+}$  are typical forms of cell injury. Reactive oxygen species, which are often produced on reperfusion of ischemic tissues, a

Early loss of selective membrane permeability leading ultimately to overt membrane damage is a cell injury (except apoptosis). The plasma membrane can be damaged by ischemia, various microbial agents, and a variety of physical and chemical agents. Several biochemical mechanisms may contribute to

**Decreased phospholipid synthesis.** The production of phospholipids in cells may be reduced, leading to decreased energy-dependent enzymatic activities. The reduced phospholipid synthesis includes the mitochondria themselves, thus exacerbating the loss of ATP. **Increased phospholipid degradation.** Associated with increased degradation of membrane phospholipids, probably due to activation of phospholipases by increased levels of cytosolic  $Ca^{2+}$ . **ROS.** Oxygen free radicals cause injury to cell membranes earlier. **Cytoskeletal abnormalities.** Cytoskeletal filaments serve as anchors connecting the membrane to the cytoskeleton. Activation of proteases by increased cytosolic  $Ca^{2+}$  may cause damage to elements of the cytoskeleton. These include unesterified free fatty acids, acyl carnitine, and lysophospholipids, catabolic products of injured cells as a result of phospholipid degradation. They have a detergent effect on the lipid bilayer of the membrane or exchange with membrane phospholipids, potentially causing electrophysiologic alterations.

The most important sites of membrane damage during cell injury are the mitochondrial membrane and lysosomes.

**Mitochondrial membrane damage.** As discussed above, damage to mitochondrial membranes leads to loss of ATP, culminating in necrosis, and release of proteins that trigger apoptotic death. **Plasma membrane damage.** Plasma membrane damage leads to loss of osmotic balance and influx of fluids and ions, as well as loss of cell metabolites that are vital for the reconstitution of ATP, thus further depleting energy stores. It also leads to leakage of their enzymes into the cytoplasm and activation of the acid hydrolases in the acidified (ischemic) cell. Lysosomes contain RNases, DNases, proteases, glucosidases, and other enzymes. Leakage leads to enzymatic digestion of cell components, and the cells die by necrosis.

### Damage to DNA and Proteins

Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (beyond the cell's stress), the cell initiates its suicide program and dies by apoptosis. A similar reaction is triggered by

be the result of inherited mutations or external triggers such as free radicals. Since these mechanisms of apoptosis, they are discussed later in the chapter.

## SUMMARY

### Mechanisms of Cell Injury

*ATP depletion:* failure of energy-dependent functions → reversible injury →  
*damage:* ATP depletion → failure of energy-dependent cellular functions →  
some conditions, leakage of proteins that cause apoptosis  
*Influx of calcium:*  
damage cellular components and may also trigger apoptosis  
*Accumulation of*  
covalent modification of cellular proteins, lipids, nucleic acids  
*Increased permeability of*  
*membranes:* may affect plasma membrane, lysosomal membranes, mitochondrial membranes  
typically culminates in necrosis  
*Accumulation of damaged DNA and misfolded proteins*  
apoptosis



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## EXAMPLES OF CELL INJURY AND NECROSIS

To illustrate the evolution and biochemical mechanisms of cell injury, we conclude this section by discussing some commonly encountered examples of reversible cell injury and necrosis.

### Ischemic and Hypoxic Injury

Ischemia, or diminished blood flow to a tissue, is the most common cause of cell injury in clinical medicine. In contrast to hypoxia, in which energy generation by anaerobic glycolysis can continue (albeit less efficiently than by oxidative pathways), ischemia also compromises the delivery of substrates for glycolysis. Consequently, anaerobic energy generation also ceases in ischemic tissues after potential substrates are exhausted or when glycolysis is inhibited by the accumulation of metabolites that would normally be removed by blood flow. Therefore, *ischemia injures tissues faster than does hypoxia*. The biochemical and structural changes in oxygen-deprived cells were discussed in detail earlier and the sequence of events is recapitulated below.

The fundamental biochemical abnormality in hypoxic cells that leads to cell injury is reduced intracellular generation of ATP, as a consequence of reduced supply of oxygen. As described above, loss of ATP leads to the *failure of many energy-dependent cellular systems, including* (1) *ion pumps* (leading to cell swelling, and influx of  $\text{Ca}^{2+}$ , with its deleterious consequences); (2) *depletion of glycogen stores*, apparent histologically by reduced staining for carbohydrates (e.g., by the periodic acid-Schiff stain), with accumulation of *lactic acid*<sub>Rx</sub>, thus lowering the intracellular pH; and (3) *reduction in protein synthesis*.

The functional consequences may be severe at this stage. For instance, heart muscle ceases to contract within 60 seconds of coronary occlusion. However, loss of contractility does not mean cell death. If hypoxia continues, worsening ATP depletion causes further deterioration, with loss of microvilli and the formation of "blebs" (see [Fig. 1-9](#)). At this time, the entire cell and its organelles (mitochondria, ER) are markedly swollen, with increased concentrations of water, sodium, and chloride and a decreased concentration of potassium. *If oxygen is restored, all of these disturbances are reversible*.

*If ischemia persists, irreversible injury and necrosis ensue*. Irreversible injury is associated with severe swelling of mitochondria, extensive damage to plasma membranes, and swelling of lysosomes (see [Fig. 1-9](#)). Massive influx of calcium into the cell may occur. Death is mainly by necrosis, but apoptosis also contributes; the apoptotic pathway is activated probably by release of pro-apoptotic molecules from leaky mitochondria. The cell's components are progressively degraded, and there is widespread leakage of cellular enzymes into the extracellular space. Finally, the dead cells may become replaced by large masses composed of phospholipids in the form of myelin figures. These are then either phagocytosed by leukocytes or degraded further into fatty acids that may become calcified.

### Ischemia-Reperfusion Injury

If cells are reversibly injured, the restoration of blood flow can result in cell recovery. However, under certain circumstances, the restoration of blood flow to ischemic but otherwise viable tissues results, paradoxically, in exacerbated and accelerated injury. As a result, tissues sustain the loss of cells *in addition to those that are irreversibly damaged at the end of the ischemic episode*. This so-called *ischemia-reperfusion injury* is a clinically important process that may contribute significantly to tissue damage in myocardial and cerebral infarctions.

Several mechanisms may account for the exacerbation of cell injury resulting from reperfusion into ischemic tissues:

New damage may be initiated during reoxygenation by increased generation of ROS from parenchymal and endothelial cells and from infiltrating leukocytes. When the supply of oxygen is increased, there may be a corresponding increase in the production of ROS, especially because mitochondrial damage leads to incomplete reduction of oxygen, and because of the action of oxidases in leukocytes, endothelial cells, or parenchymal cells. Cellular antioxidant defense mechanisms may also be compromised by ischemia, favoring the accumulation of free radicals. Ischemic injury is associated with *inflammation*, which may increase with reperfusion because of increased influx of leukocytes and plasma proteins. The products of activated leukocytes may cause additional tissue injury ([Chapter 2](#)). Activation of the *complement system* may also contribute to ischemia-reperfusion injury. Some antibodies have a propensity to deposit in ischemic tissues for unknown reasons, and when blood flow is resumed, complement proteins bind to the deposited antibodies, are activated, and exacerbate the cell injury and inflammation.

### Chemical (Toxic) Injury

Chemicals induce cell injury by one of two general mechanisms.

*Some chemicals act directly by combining with a critical molecular component or cellular organelle.* For example, in mercuric chloride poisoning, mercury binds to the sulfhydryl groups of various cell membrane proteins, causing inhibition of ATP-dependent transport and increased membrane permeability. Many antineoplastic chemotherapeutic agents also induce cell damage by direct cytotoxic effects. In such instances, *the greatest damage is sustained by the cells that use, absorb, excrete, or concentrate the compounds.* Many other chemicals are not intrinsically biologically active but must be first converted to reactive toxic metabolites, which then act on target cells. This modification is usually accomplished by the P-450 mixed-function oxidases in the smooth endoplasmic reticulum of the liver and other organs. Although the metabolites might cause membrane damage and cell injury by direct covalent binding to protein and lipids, the most important mechanism of cell injury involves the formation of free radicals. *Carbon tetrachloride* ( $\text{CCl}_4$ , which was used widely in the dry cleaning industry but is now banned) and the analgesic *acetaminophen*<sup>®</sup> belong in this category.  $\text{CCl}_4$ , for example, is converted to the toxic free radical  $\text{CCl}_3^\bullet$ , principally in the liver. The free radicals cause autocatalytic membrane phospholipid peroxidation, with rapid breakdown of the ER. In less than 30 minutes after exposure to  $\text{CCl}_4$ , there is a decline in hepatic protein synthesis of enzymes and plasma proteins; within 2 hours, swelling of the smooth endoplasmic reticulum and dissociation of ribosomes from the smooth endoplasmic reticulum have occurred. There is reduced lipid export from the hepatocytes, as a result of their inability to synthesize apoprotein to form complexes with triglycerides and thereby facilitate lipoprotein secretion; the result is the "fatty liver" of  $\text{CCl}_4$  poisoning. Mitochondrial injury follows, and subsequently diminished ATP stores result in defective ion transport and progressive cell swelling; the plasma membranes are further damaged by fatty aldehydes produced by lipid peroxidation in the ER. The end result can be calcium influx and eventually cell death.







## APOPTOSIS

*Apoptosis* is a pathway of cell death that is induced by a tightly regulated suicide program in which the cell is capable of degrading the cells' own nuclear DNA and nuclear and cytoplasmic proteins. Fragmentation of the nucleus, giving the appearance that is responsible for the name (*apoptosis*, "falling off"). The plasma membrane remains intact but the membrane is altered in such a way that the cell and its fragments become avid targets for phagocytosis and are cleared before its contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory response. Thus, apoptosis differs from necrosis, which is characterized by loss of membrane integrity, enzyme leakage, and frequently a host reaction (see [Fig. 1-6](#) and [Table 1-1](#)). However, apoptosis and necrosis induced by some pathologic stimuli may progress to necrosis.

### Causes of Apoptosis

Apoptosis occurs normally in many situations, and serves to eliminate potentially harmful cells and damaged cells. It is also a pathologic event when cells are damaged beyond repair, especially when the damage is severe. In these situations, the irreparably damaged cell is eliminated.

### Apoptosis in Physiologic Situations

*Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed or are potentially harmful.* It is important in the following physiologic situations:

*The programmed destruction of cells during embryogenesis*, including implantation, organogenesis, and metamorphosis. The term "programmed cell death" was originally coined to denote death occurring during the development of an organism. Apoptosis is a generic term for this pattern of cell death and is often used interchangeably with "programmed cell death." *Involution of hormone-dependent tissues*, such as endometrial cell breakdown during the menstrual cycle, and regression of the lactating breast. *Elimination of proliferating cell populations*, such as intestinal crypt epithelia, so as to maintain a constant population. *Elimination of cells*, such as neutrophils in an acute inflammatory response, and lymphocytes in chronic inflammation. In these situations, cells undergo apoptosis because they are deprived of necessary survival factors. *Elimination of potentially harmful self-reactive lymphocytes*, either before or after they have caused damage in order to prevent reactions against one's own tissues ([Chapter 5](#)). *Cell death induced by cytotoxic mechanisms* against viruses and tumors that serves to kill and eliminate virus-infected and tumor cells.

### Apoptosis in Pathologic Conditions

*Apoptosis eliminates cells that are genetically altered or injured beyond repair without eliciting a significant inflammatory response.* Death by apoptosis is responsible for loss of cells in a variety of pathologic conditions.

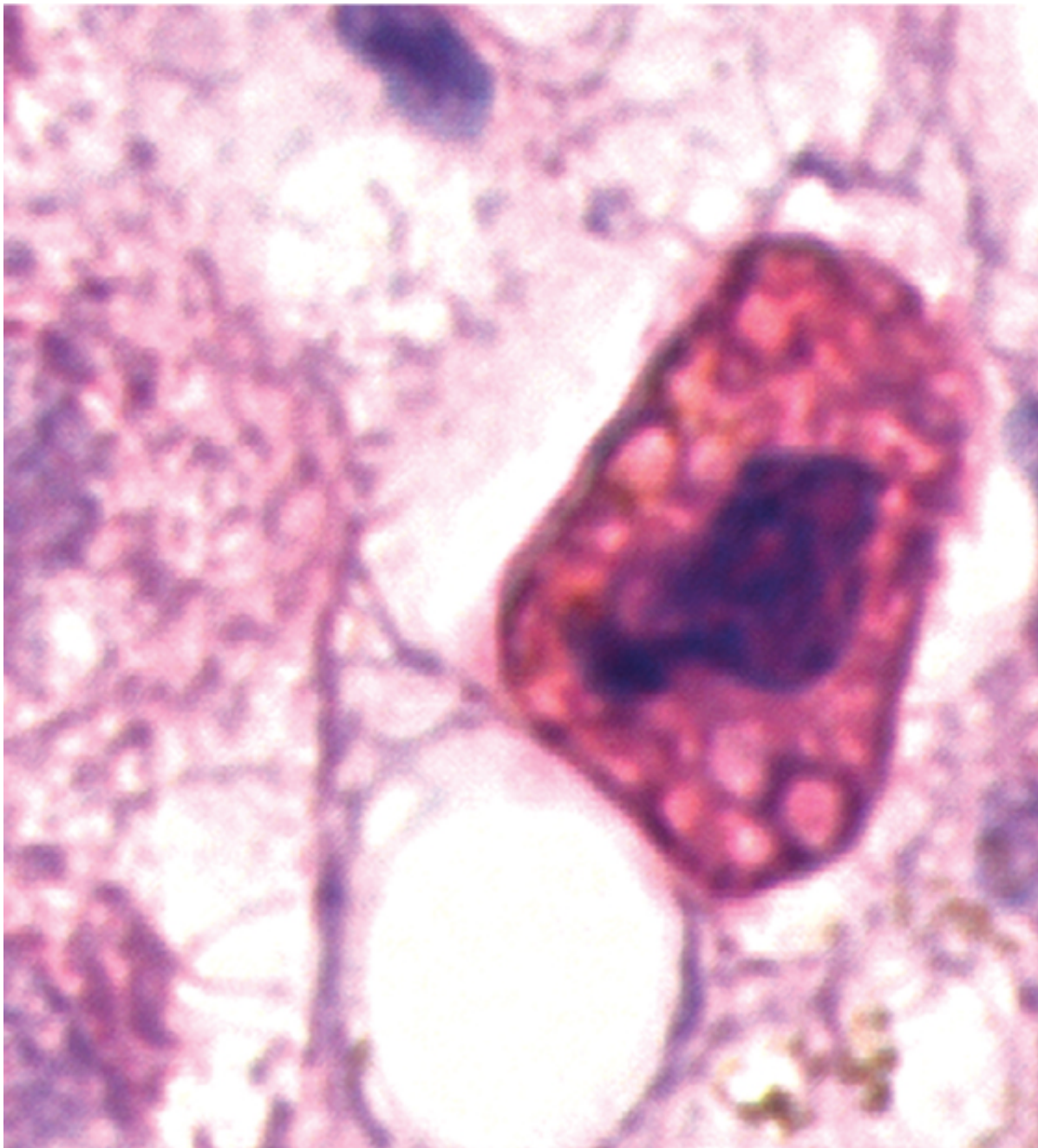
*DNA damage.* Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia can cause apoptosis or via production of free radicals. If repair mechanisms cannot cope with the injury, the cell undergoes apoptosis. In these situations, elimination of the cell may be a better alternative than risking malignant transformation. These injurious stimuli cause apoptosis if the injury is severe enough to result in necrotic cell death. Inducing apoptosis of cancer cells is a desired effect of chemotherapy. *Accumulation of misfolded proteins.* Improperly folded proteins may be due to mutations in genes encoding these proteins or because of extrinsic factors, such as damage caused by heavy metals. Accumulation of these proteins in the ER leads to a condition called *ER stress*, which culminates in apoptosis. *Infections*, particularly viral infections, in which loss of infected cells is largely due to apoptosis. For example, in HIV infection (as in adenovirus and human immunodeficiency virus infections) or by the host immune response in hepatitis. *Pathologic atrophy in parenchymal organs after duct obstruction*, such as occurs in chronic pancreatitis.

### **Mechanisms of Apoptosis**

Apoptosis is an active enzymatic process in which nucleoproteins are broken down and then the cellular components are released. At the molecular mechanisms, it is useful to review the morphology of this pathway of cell death.

#### **Morphology**

In H&E-stained tissue sections, apoptotic cells may appear as round or oval masses with condensed, eosinophilic cytoplasm (Fig. 1-22). Nuclei show various stages of chromatin condensation and, ultimately, karyorrhexis; at the molecular level this is reflected in fragmentation into small-sized pieces. The cells rapidly shrink, form cytoplasmic buds, and fragment into apoptotic bodies of membrane-bound vesicles of cytosol and organelles (see Fig. 1-6). Because the apoptotic bodies are extruded and phagocytosed without eliciting an inflammatory response, even submicroscopic apoptotic bodies are histologically undetectable.



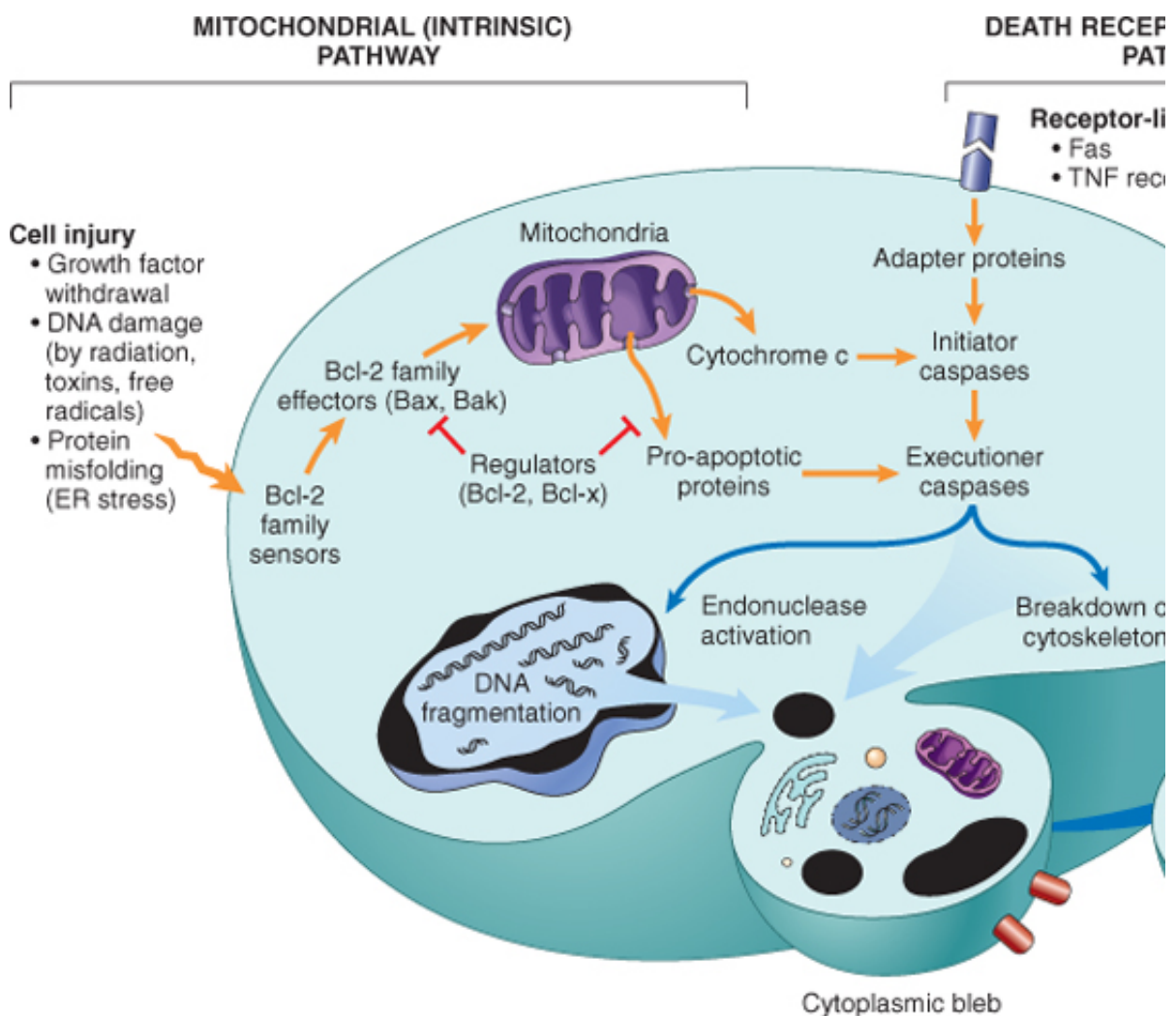


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Figure 1-22 Apoptosis of a liver cell in viral hepatitis. The cell is reduced in size and contains brightly eosinophilic

The fundamental event in apoptosis is the activation of enzymes called *caspases* (so named because they cleave proteins after aspartic residues). Activated caspases cleave numerous targets, culminating in the destruction of DNA and other enzymes that presumably destroy nucleoproteins and cytoskeletal proteins. The process is a finely tuned balance between pro- and anti-apoptotic molecular pathways. Two distinct pathways converge on the activation of caspases: the *mitochondrial pathway* and the *death receptor pathway*. Although these pathways can interact, they involve different molecules, and serve distinct roles in physiology and disease (Fig. 1-23).

#### The Mitochondrial (Intrinsic) Pathway of Apoptosis



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Figure 1-23 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and the molecules involved. The induction of apoptosis is dependent on a balance between pro- and anti-apoptotic signals and intracellular factors that induce apoptotic cell death, and the anti-apoptotic proteins that inhibit mitochondrial leakiness and cytochrome c release. Cytochrome c function as regulators of mitochondrial apoptosis.

Mitochondria contain several proteins that are capable of inducing apoptosis; these proteins include Bcl-2, Bcl-xL, and Bcl-2L1. The choice between cell survival and death is determined by the balance of these proteins, which is controlled by a family of more than 20 proteins, the prototype of which is Bcl-2.

mitochondria, which is controlled by a family of more than 20 proteins, the prototype of which is Bcl-2. Factors and trophic hormones, or are exposed to agents that damage DNA, or accumulate unacceptably, a group of sensors is activated. Some of these sensors, which are members of the Bcl-2 family, in the family called Bax and Bak, which dimerize, insert into the mitochondrial membrane, and form pores through which and other mitochondrial proteins escape into the cytosol. Other related sensors inhibit the anti-apoptotic proteins (see below), with the same end result—the leakage of mitochondrial proteins. Cytochrome c, together with other proteins block the activities of caspase antagonists that function as physiologic inhibitors of the caspase cascade, ultimately leading to nuclear fragmentation. If cells are exposed to apoptotic signals, they synthesize antiapoptotic members of the Bcl-2 family, the two main ones of which are Bcl-2 and Bcl-x<sub>L</sub>, which antagonize Bax and Bak, and thus limit the escape of mitochondrial pro-apoptotic proteins. Cells that receive apoptotic signals activate the pro-apoptotic proteins but also show reduced levels of Bcl-2 and Bcl-x<sub>L</sub>, thus further promoting the mitochondrial pathway. The mitochondrial pathway seems to be the pathway that is responsible for most situations of apoptosis.

### *The Death Receptor (Extrinsic) Pathway of Apoptosis*

Many cells express surface molecules, called death receptors, that trigger apoptosis. Most of these are members of the TNF receptor family that contain in their cytoplasmic regions a conserved "death domain," which mediates interaction with other proteins. The prototypic death receptors are the type I TNF receptor and Fas receptor, a membrane protein expressed mainly on activated T lymphocytes. When these T cells recognize FasL-expressing cells, they cross-link by the FasL and they bind adapter proteins, which in turn bind caspase-8. Clustering and activation of caspase-8, thus initiating the caspase cascade. In many cell types caspase-8 may cleave and activate a family member called Bid, thus feeding into the mitochondrial pathway. The combined activation of both pathways leads to apoptosis. Cellular proteins, notably a caspase antagonist called FLIP, block activation of caspases downstream of the death receptor pathway. Some viruses produce homologues of FLIP, and it is suggested that this is a mechanism that viruses use to evade the death receptor pathway. The death receptor pathway is involved in elimination of self-reactive lymphocytes and in killing of target cells.

### *Clearance of Apoptotic Cells*

Apoptotic cells undergo several changes in their membranes that promote their phagocytosis. In normal cells, phospholipids are asymmetrically distributed, with phosphatidylserine (PS) on the inner leaflet of the plasma membrane, but in apoptotic cells this phospholipid "flips" out and is exposed on the outer membrane, where it is recognized by macrophages. Cells that are dying by apoptosis also secrete factors that attract macrophages. This facilitates prompt clearance of the dead cells before they undergo secondary membrane damage (which can result in inflammation). Some apoptotic bodies express adhesive glycoproteins that are recognized by macrophages themselves may produce proteins that bind to apoptotic cells (but not to live cells). Numerous macrophage receptors have been shown to be involved in the binding and engulfment of apoptotic cells. The phagocytosis of apoptotic cells is so efficient that dead cells disappear without leaving a trace, and no inflammation occurs.

Although we have emphasized the distinctions between necrosis and apoptosis, these two forms of cell death overlap mechanistically. For instance, DNA damage (seen in apoptosis) activates an enzyme called poly(ADP-ribose) polymerase (PARP), which depletes cellular supplies of nicotinamide adenine dinucleotide, leading to a fall in ATP levels and ultimately to cell death. In situations such as ischemia, it has been suggested that early cell death can be partly attributed to the type of cell death late, with worsening ischemia.

### **Examples of Apoptosis**

Cell death in many situations is known to be caused by apoptosis, and the selected examples listed below illustrate the pathway in normal physiology and in disease.

#### *Growth Factor Deprivation*

Hormone-sensitive cells deprived of the relevant hormone, lymphocytes that are not stimulated by antigen, or neurons deprived of nerve growth factor die by apoptosis. In all these situations, apoptosis is triggered by a signal that is attributable to activation of pro-apoptotic members of the Bcl-2 family and decreased synthesis of anti-apoptotic members.

#### *DNA Damage*

Exposure of cells to radiation or chemotherapeutic agents induces DNA damage, and if this is too severe, the cell undergoes apoptosis. When DNA is damaged, the p53 protein accumulates in cells. It first arrests the cell cycle (by inhibiting the



(Chapter 6). However, if the damage is too great to be repaired successfully, p53 triggers apoptosis ultimately activate Bax and Bak, and by stimulating synthesis of pro-apoptotic members of the Bcl (as it is in certain cancers), it is incapable of inducing apoptosis, so that cells with damaged DNA DNA damage may result in mutations or translocations that lead to neoplastic transformation (Chapter 6).

#### *Accumulation of Misfolded Proteins*

During normal protein synthesis, chaperones in the ER control the proper folding of newly synthesized polypeptides are ubiquitinated and targeted for proteolysis. If, however, unfolded or misfolded proteins are produced due to inherited mutations or stresses, they induce "ER stress" that triggers a number of cellular responses. This response activates signaling pathways that increase the production of chaperones reducing the levels of misfolded proteins in the cell. However, if this response is unable to cope with the accumulation of misfolded proteins, the result is the activation of caspases that lead to apoptosis. Intracellular accumulation of misfolded proteins, due to mutations, aging, or unknown environmental factors, is now recognized as a feature of a number of diseases, including Alzheimer, Huntington, and Parkinson diseases, and possibly type II diabetes. Deprivation of glucose and heat, also result in protein misfolding, culminating in cell injury and death.

#### *Apoptosis of Self-Reactive Lymphocytes*

Lymphocytes capable of recognizing self antigens are normally produced in all individuals. If these cells are not eliminated by apoptosis, they can cause autoimmune diseases. Both the mitochondrial pathway and the Fas death receptor pathway have been implicated in the apoptosis of self-reactive lymphocytes (Chapter 5). Failure of apoptosis of self-reactive lymphocytes is one of the causes of autoimmune diseases.

#### *Cytotoxic T Lymphocyte-Mediated Apoptosis*

Cytotoxic T lymphocytes (CTLs) recognize foreign antigens presented on the surface of infected cells. Upon activation, CTL granule proteases called *granzymes* enter the target cells. Granzymes are capable of activating cellular caspases. In this way, the CTL kills target cells by directly inducing the efflux of cytochrome c from mitochondria or death receptors. CTLs also express FasL on their surface and may kill target cells by engaging Fas receptors.

### **SUMMARY** **Apoptosis**

Regulated mechanism of cell death that serves to eliminate unwanted and injured cells with the least possible host reaction. Characterized by: enzymatic degradation initiated by caspases; and recognition and removal of dead cells by phagocytosis. Two main pathways:

*Mitochondrial (intrinsic) pathway* is triggered by loss of survival signals, accumulation of misfolded proteins (ER stress); associated with leakage of cytochrome c from mitochondrial membrane into the cytoplasm, where the activation; inhibited by anti-apoptotic members of the Bcl family, which inhibit the activation. *Death receptor (extrinsic) pathway* is triggered by engagement of death receptors (members of the TNF receptor family) on the cell surface.

This description of apoptosis concludes the discussion of cell injury and cell death. As we have seen, many common diseases are caused by cell injury. We end this chapter with brief considerations of three other processes: calcium overload, oxidative stress, and extracellular deposition of calcium, both of which are often associated with cell injury.







## INTRACELLULAR ACCUMULATIONS

Under some circumstances cells may accumulate abnormal amounts of various substances, which varying degrees of injury. The substance may be located in the cytoplasm, within organelles (typical may be synthesized by the affected cells or may be produced elsewhere).

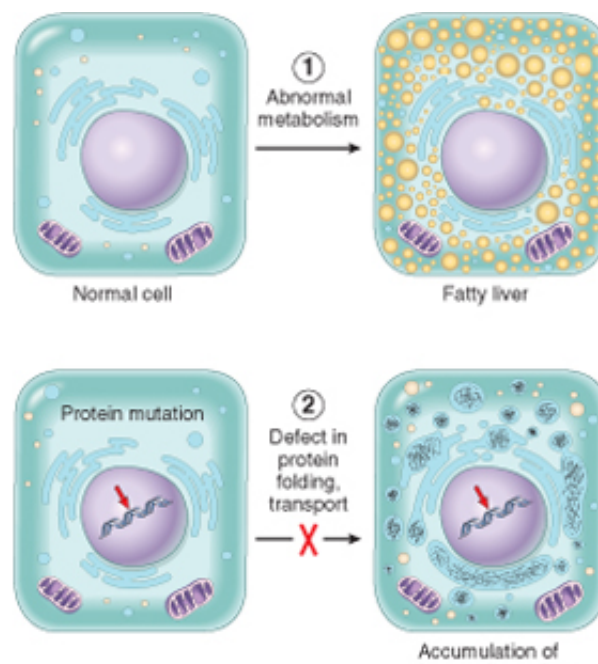
There are three main pathways of abnormal intracellular accumulations (Fig. 1-24):

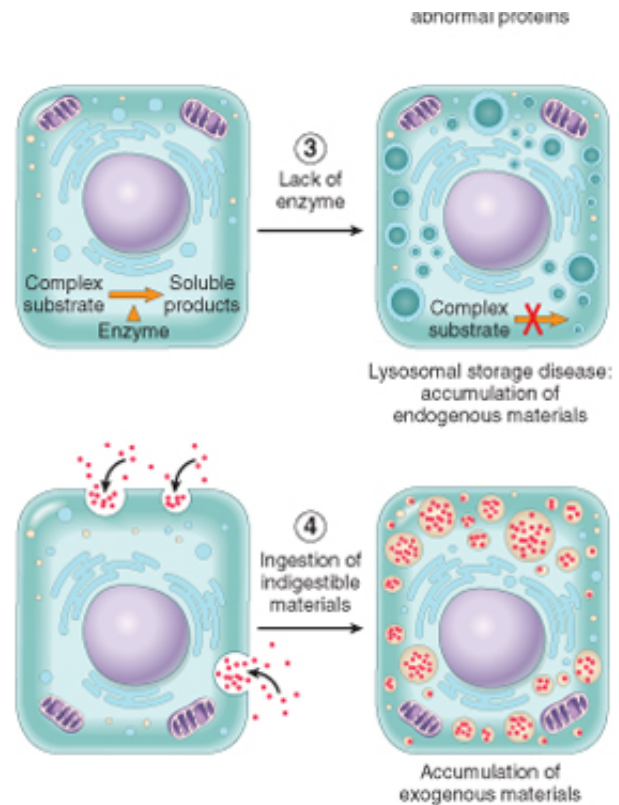
A normal substance is produced at a normal or an increased rate, but the metabolic rate is this type of process is fatty change in the liver. A normal or an abnormal endogenous substance acquired defects in its folding, packaging, transport, or secretion. Mutations that cause defective accumulation of proteins (e.g.,  $\alpha_1$ -antitrypsin deficiency). An inherited defect in an enzyme that metabolite. The resulting disorders are called storage diseases (Chapter 7). An abnormal substance accumulates because the cell has neither the enzymatic machinery to degrade the substance. Accumulations of carbon or silica particles are examples of this type of alteration.

### *Fatty Change (Steatosis)*

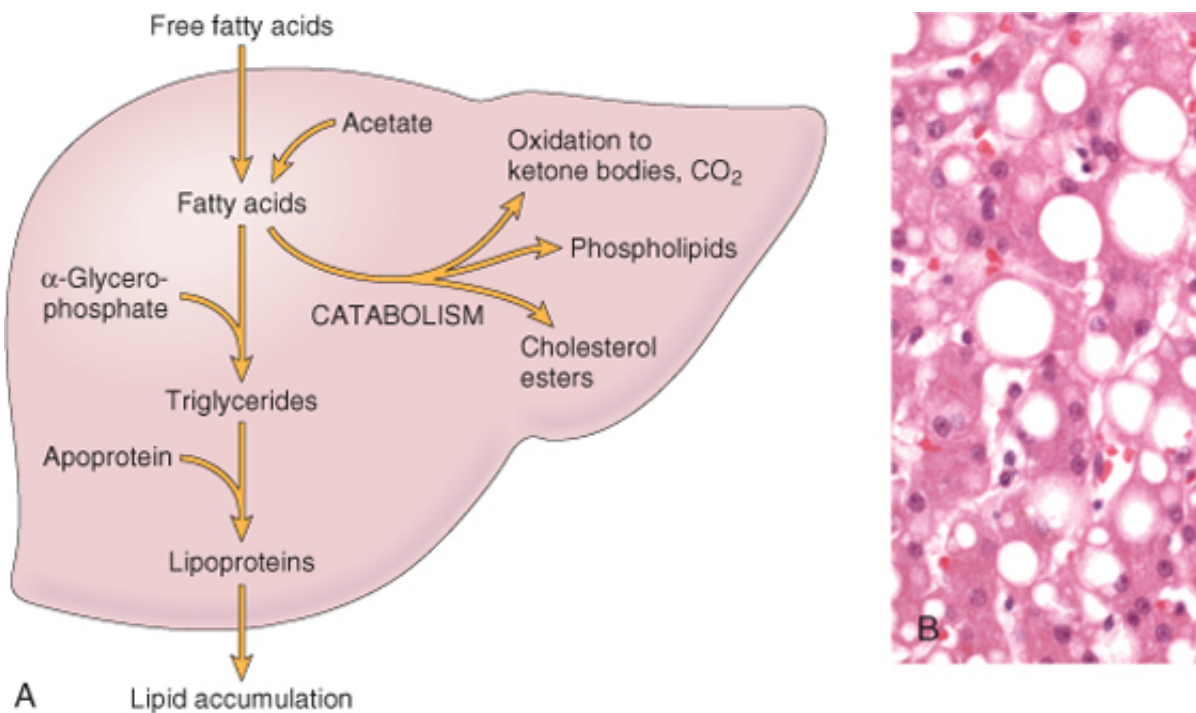
*Fatty change* refers to any abnormal accumulation of triglycerides within parenchymal cells. It is not the major organ involved in fat metabolism, but it may also occur in heart, skeletal muscle, kidney caused by toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia. *Alcohol abuse and the most common causes of fatty change in the liver* (fatty liver) in industrialized nations.

Free fatty acids from adipose tissue or ingested food are normally transported into hepatocytes, where converted into cholesterol or phospholipids, or oxidized to ketone bodies (Fig. 1-25A). Some fatty acids enter the hepatocytes as well. Egress of the triglycerides from the hepatocytes requires the formation of lipoproteins, which are able to enter the circulation (Chapter 7). Excess accumulation of triglycerides from fatty acid entry to lipoprotein exit, thus accounting for the occurrence of fatty liver after diverse causes (alcohol) alter mitochondrial and SER function and thus inhibit fatty acid oxidation;  $\text{CCl}_4$  and protein apoproteins; anoxia inhibits fatty acid oxidation; and starvation increases fatty acid mobilization from





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 Figure 1-24 Mechanisms of intracellular accumulation. (1) Abnormal metabolism, as in fatty change in the liver. (2) and transport, so that defective molecules accumulate intracellularly. (3) A deficiency of critical enzymes responsible for the breakdown of complex substrates to accumulate in lysosomes, as in lysosomal storage diseases. (4) An inability to degrade phagocytosed



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 Figure 1-25 Fatty change in the liver. (A) Metabolic pathways of lipids in the liver. (B) Microscopic image of liver tissue showing lipid accumulation (steatosis).

Figure 1-25 Fatty liver. **A**, The possible mechanisms leading to accumulation of triglycerides in fatty liver. Decreased secretion can lead to lipid accumulation. **B**, High-power detail of fatty change of the liver. In most cells the well-preserved cytoplasm about the fat vacuole. (**B**, Courtesy of Dr. James Crawford, Department of Pathology, University of F

The significance of fatty change depends on the cause and severity of the accumulation. When mild, it has little effect on liver function. More severe fatty change may transiently impair cellular function, but unless some vital function is impaired (e.g., in  $\text{CCl}_4$  poisoning), fatty change is reversible. In the severe form, fatty change may be a lesion in a serious liver disease called nonalcoholic steatohepatitis ([Chapter 16](#)).

### Morphology

In any site, fatty accumulation appears as clear vacuoles within parenchymal cells. Special techniques are required to distinguish fat from intracellular water or glycogen, which also appears as clear vacuoles but have a different significance. To identify fat microscopically, tissues are often frozen and sectioned without the organic solvents typically used in sample preparation. Usually, tissues are stained with Sudan IV or oil red O (these stain fat orange-red). Glycogen may be identified as polysaccharides using the periodic acid-Schiff stain (which stains glycogen red-violet). If a stain for either fat or glycogen, they are presumed to be composed mostly of water.

Fatty change is most commonly seen in the liver and the heart. Mild fatty change in the liver has little effect on the gross appearance. With increasing accumulation, the organ enlarges and becomes greasy. In extreme cases, it may weigh 3 to 6 kg (1.5-3 times the normal weight) and is very greasy. Early fatty change is seen by light microscopy as small fat vacuoles in the cytoplasm. In later stages, the vacuoles coalesce to create cleared spaces that displace the nucleus to the periphery ([Fig. 1-25B](#)). Occasionally contiguous cells rupture, and the enclosed fat is released, forming so-called fatty cysts.

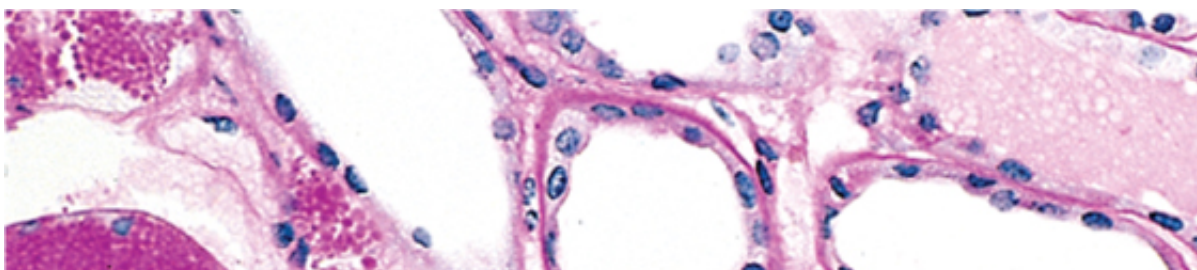
In the **heart**, lipid is found in the form of small droplets, occurring in one of two patterns. Mild hypoxia (as in profound anemia) results in focal intracellular fat deposits, creating a mottled, yellowed myocardium alternating with bands of darker, red-brown, uninvolved heart muscle. A more severe pattern of fatty change is produced by more profound hypoxia or by some form of systemic disease (e.g., diphtheria) and shows more uniformly affected myocytes.

### Cholesterol and Cholesteryl Esters

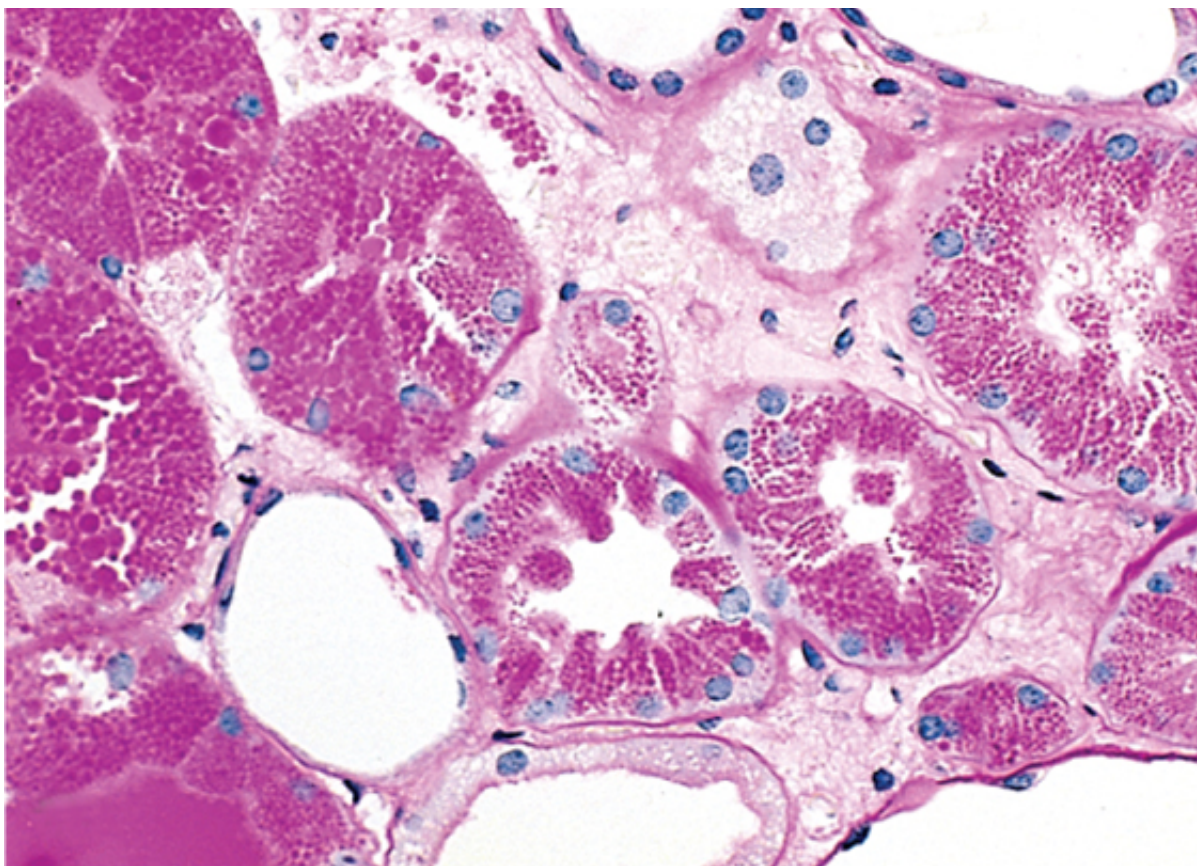
Cellular cholesterol metabolism is tightly regulated to ensure normal cell membrane synthesis with cholesterol. However, phagocytic cells may become overloaded with lipid (triglycerides, cholesterol, and cholesterol esters) in various pathologic processes.

Macrophages in contact with the lipid debris of necrotic cells or abnormal (e.g., oxidized) forms of cholesterol are filled with minute, membrane-bound vacuoles of phagocytosed lipid. These macrophages may be filled with minute, membrane-bound vacuoles of their cytoplasm (*foam cells*). In *atherosclerosis*, smooth muscle cells and macrophages are filled with cholesterol and cholesteryl esters; these give atherosclerotic plaques their characteristic yellow color. In hereditary and acquired hyperlipidemic syndromes, macrophages accumulate in the subepithelial connective tissue of skin or in tendons, clusters of these foamy macrophages are present.

### Proteins







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Figure 1-26 Protein reabsorption droplets in the renal tubular epithelium. (Courtesy of Dr. Helmut Rennke, Dep  
Hospital, Boston, Massachusetts.)

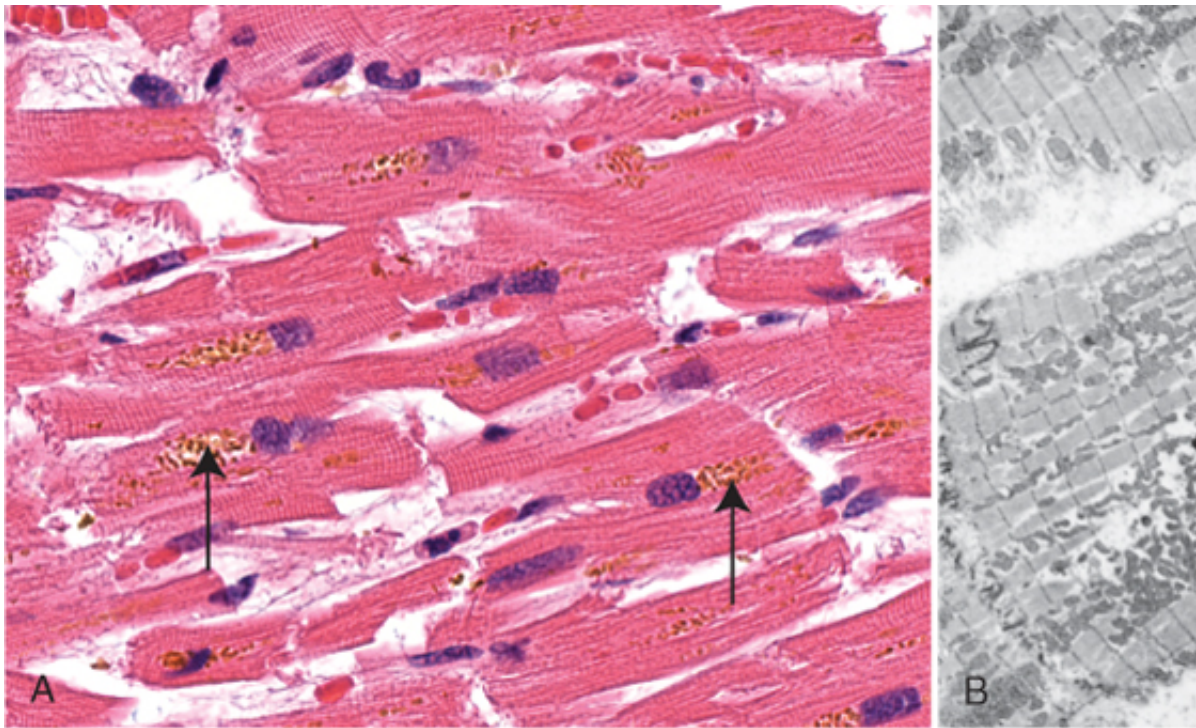
Morphologically visible protein accumulations are much less common than lipid accumulations; they are presented to the cells or because the cells synthesize excessive amounts. In the kidney, for example, proteins that are filtered through the glomerulus are normally reabsorbed by pinocytosis in the proximal convoluted tubules. In the case of protein leakage across the glomerular filter (e.g., nephrotic syndrome), there is a much larger real load. These protein droplets fuse with lysosomes, resulting in the histologic appearance of pink, hyaline droplets. The process is reversible; if the proteinuria abates, the protein droplets are metabolized and disappear. An accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells is called *Russell bodies*.

Accumulations of intracellular proteins are also seen in certain types of cell injury. For example, there is an eosinophilic cytoplasmic inclusion in liver cells that is highly characteristic of alcoholic liver disease. This inclusion is composed predominantly of aggregated intermediate filaments that presumably resist degradation. In the brain in Alzheimer disease is an aggregated protein inclusion that contains microtubule-associated protein 1 (MAP-1) of a disrupted neuronal cytoskeleton ([Chapter 23](#)).

### Glycogen

Excessive intracellular deposits of glycogen are associated with abnormalities in the metabolism of glucose. In uncontrolled diabetes mellitus, the prime example of abnormal [glucose](#) metabolism, glycogen accumulates in cardiac myocytes, and  $\beta$  cells of the islets of Langerhans. Glycogen also accumulates within cells in various storage disorders collectively referred to as *glycogen storage diseases*, or *glycogenoses* ([Chapter 7](#)). In these disorders, either the synthesis or breakdown of glycogen result in massive stockpiling, with secondary injury and cell death.

### Pigments



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 Figure 1-27 Lipofuscin granules in a cardiac myocyte. **A**, Light microscopy (deposits indicated by arrows). **B**, intralysosomal location.

Pigments are colored substances that are either exogenous, coming from outside the body, or endogenous, produced by the body itself.

The most common exogenous pigment is *carbon* (an example is coal dust), a ubiquitous air pollutant that is phagocytosed by alveolar macrophages and transported through lymphatic channels to lymph nodes. Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma. Large accumulations may induce emphysema or a fibroblastic reaction that can result in a serious pneumoconiosis ([Chapter 13](#)). Endogenous pigments include lipofuscin, melanin, and hemosiderin. Lipofuscin, or "wear-and-tear pigment," is an insoluble brownish-yellow granular intracellular material that accumulates (particularly the heart, liver, and brain) as a function of age or atrophy. Lipofuscin represents the accumulation of oxidized polyunsaturated lipids that derive from the free radical-catalyzed peroxidation of polyunsaturated lipids of subcellular membranes, but is important as a marker of past free-radical injury. The brown pigment ([Fig. 1-27](#)), which gives an aged appearance to the tissue that is called *brown atrophy*. By electron microscopy, the pigment is seen as electron-dense granules ([Fig. 1-27B](#)). *Melanin* is an endogenous, brown-black pigment produced in melanocytes through the oxidation of tyrosine to dihydroxyphenylalanine. It is synthesized exclusively by melanocytes to serve as a screen against harmful ultraviolet radiation. Although melanocytes are the only source of melanin in the skin, keratinocytes can accumulate the pigment (e.g., in freckles), as can dermal macrophages. *Hemosiderin* is a golden yellow to brown pigment that accumulates in tissues when there is a local or systemic excess of iron. It is stored within cells in association with the protein *apoferritin*, forming ferritin micelles. Hemosiderin aggregates of these ferritin micelles, readily visualized by light and electron microscopy; the characteristic brown color is demonstrated by the Prussian blue histochemical reaction ([Fig. 1-28](#)). Although hemosiderin accumulation is normal in the mononuclear phagocytes of the bone marrow, spleen, and liver, excessive accumulation is abnormal. Local excesses of iron, and consequently of hemosiderin, result from hemorrhage. After lysis of the erythrocytes at the site of hemorrhage, the red cell debris is phagocytosed by macrophages. Hemoglobin content is then catabolized by lysosomes with accumulation of the heme iron in the form of hemosiderin. The original red-blue color of the bruise passes through shades of green-blue by the local formation of biliverdin (green bile) and bilirubin (red bile).



hemoglobin accumulate as golden-yellow hemosiderin. Whenever there is systemic overload of iron in many organs and tissues, a condition called *hemosiderosis* ([Chapter 12](#)). It is found at first in the liver, bone marrow, spleen, and lymph nodes and in scattered macrophages throughout the body. With accumulation, parenchymal cells throughout the body (but principally the liver, pancreas, heart, and skin) become "bronzed" with accumulating pigment. Hemosiderosis occurs in the setting of (1) increased utilization of iron, (2) hemolytic anemias, and (3) transfusions (the transfused red cells contribute to the iron load). In instances of systemic hemosiderosis, the iron pigment does not damage the parenchymal cells. In more impressive accumulation ([Fig. 1-28](#)). However, more extensive accumulations of iron are seen in *hemochromatosis* ([Chapter 16](#)), with tissue injury including liver fibrosis, heart failure, and diabetes mellitus.

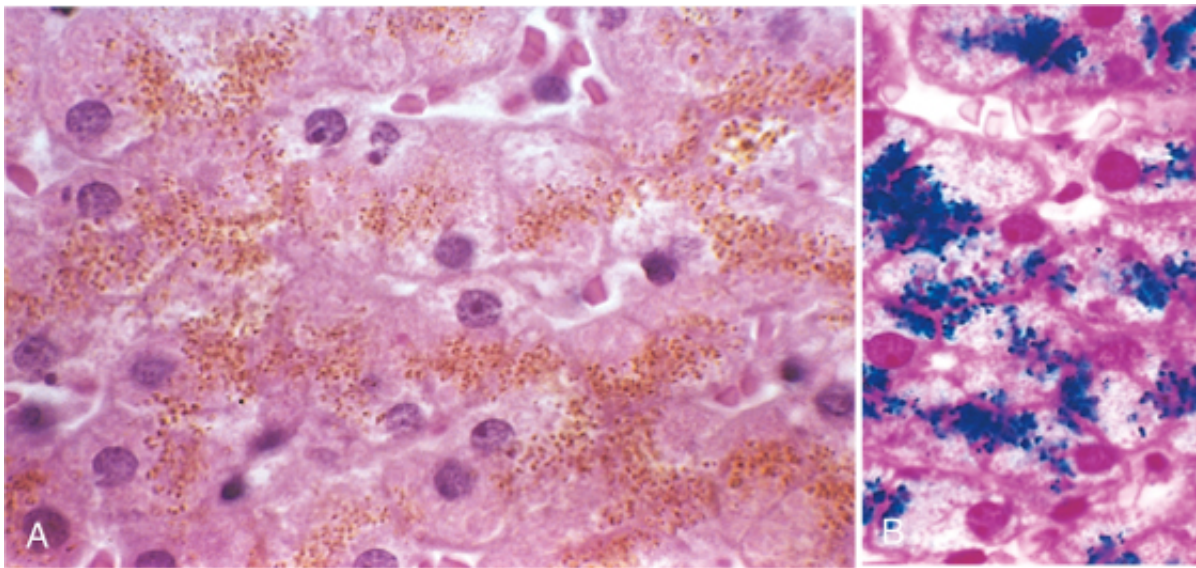




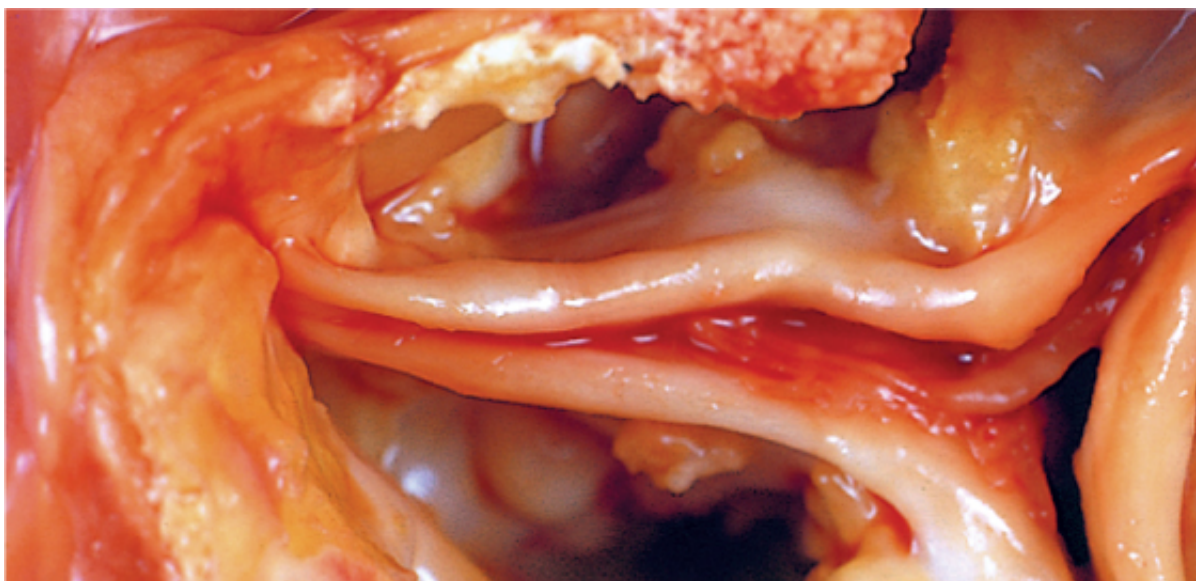
## PATHOLOGIC CALCIFICATION

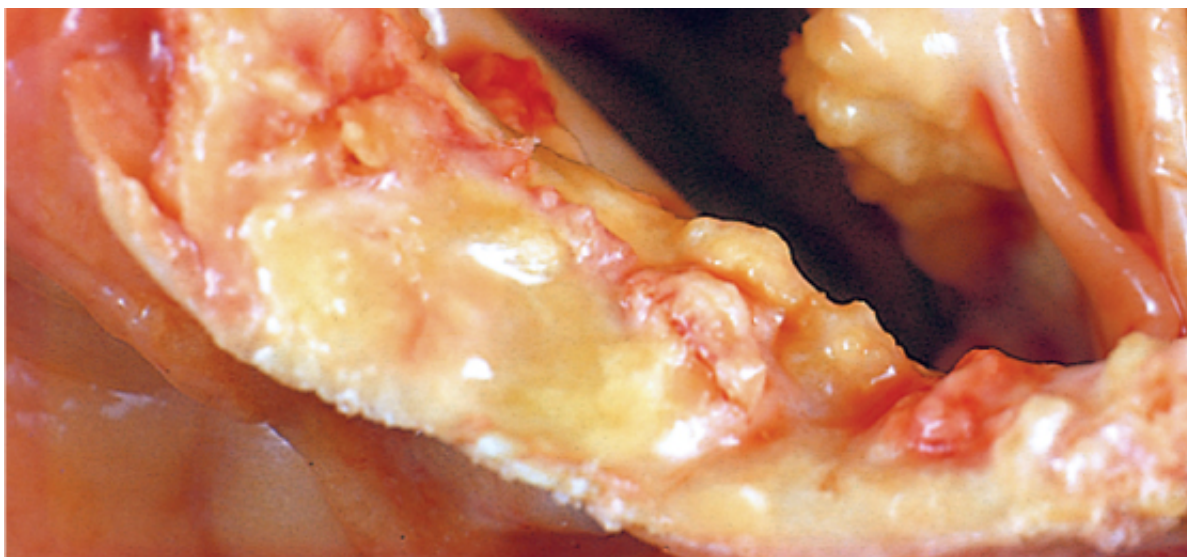
Pathologic calcification is a common process in a wide variety of disease states; it implies the abnormal deposition of calcium salts together with smaller amounts of iron, magnesium, and other minerals. When the deposition occurs in the absence of calcium metabolic derangements (i.e., with normal calcium metabolism) it is known as *dystrophic calcification*; it occurs in the absence of calcium metabolic derangements (i.e., with normal calcium metabolism) it is known as *metastatic calcification* and almost always in the presence of a calcium metabolism abnormality (hypercalcemia). It should be noted that while hypercalcemia is not a prerequisite for metastatic calcification, it can exacerbate it.

### *Dystrophic Calcification*



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Figure 1-28 Hemosiderin granules in liver cells. **A**, H&E section showing golden-brown, finely granular pigment





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Figure 1-29 Calcification of the aortic valve. A view looking down onto the unopened aortic valve in a heart with c thickened and fibrotic. Behind each cusp are large, irregular masses of dystrophic calcification that will

Dystrophic calcification is encountered in areas of necrosis of any type. It is virtually inevitable in t atherosclerosis, associated with intimal injury in the aorta and large arteries and characterized by Although dystrophic calcification may be an incidental finding indicating insignificant past cell injur dysfunction. For example, calcification can develop in aging or damaged heart valves, resulting in Dystrophic calcification of the aortic valves is an important cause of aortic stenosis in the elderly (

### Morphology

Regardless of the site, calcium salts are grossly seen as fine white granules or clu deposits. Sometimes a tuberculous lymph node is essentially converted to radio-of calcification appears as intracellular and/or extracellular basophilic deposits. In tim be formed in the focus of calcification.

The pathogenesis of dystrophic calcification involves *initiation* (or nucleation) and *propagation*, bo extracellular; the ultimate end product is the formation of crystalline *calcium phosphate*. Initiation i bound vesicles about 200 nm in diameter; in normal cartilage and bone they are known as *matrix* they derive from degenerating cells. It is thought that calcium is initially concentrated in these vesi phospholipids, while phosphates accumulate as a result of the action of membrane-bound phosph calcification occurs in the mitochondria of dead or dying cells that have lost their ability to regulate either location, propagation of crystal formation occurs. This is dependent on the concentration of spaces, the presence of mineral inhibitors, and the degree of collagenization, which enhances the

### Metastatic Calcification

Metastatic calcification can occur in normal tissues whenever there is hypercalcemia. The four ma *increased secretion of parathyroid hormone*, due to either primary parathyroid tumors or productic by other malignant tumors; (2) *destruction of bone* due to the effects of accelerated turnover (e.g., tumors (increased bone catabolism associated with multiple myeloma, leukemia, or diffuse skelet; *disorders* including vitamin D intoxication and *sarcoidosis* (in which macrophages activate a vitam which phosphate retention leads to *secondary hyperparathyroidism*.

### Morphology

Metastatic calcification can occur widely throughout the body but principally affects the vasculature, kidneys, lungs, and gastric mucosa. The calcium deposits morphc described in dystrophic calcification. Although they do not generally cause clinical (

calcifications in the lungs may produce remarkable radiographs and respiratory distress. Deposits in the kidney (**nephrocalcinosis**) can cause renal damage.

## SUMMARY

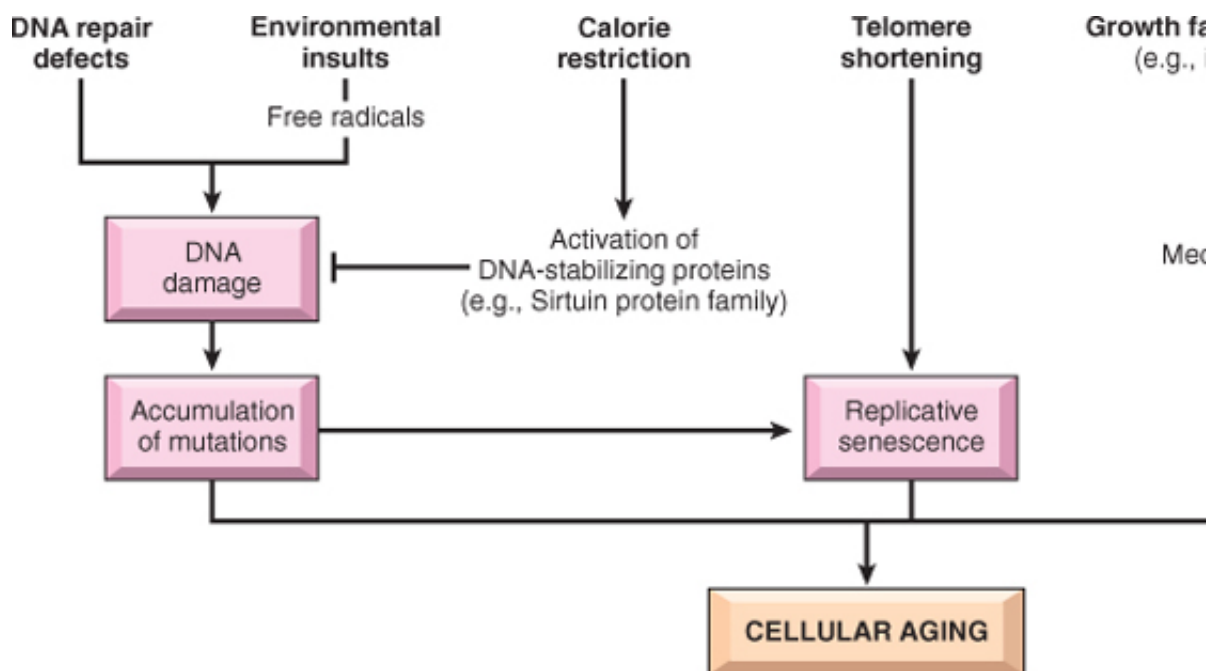
### Abnormal Intracellular Depositions and Calcifications

Abnormal deposits of materials in cells and tissues are the result of excessive transport or catabolism. Depositions of *lipids*:

*Fatty change*: accumulation of free triglycerides in cells, resulting from defective transport (often because of defects in synthesis of transport proteins) or reversible cell injury. *Cholesterol deposition*: result of defective catabolism; in macrophages and smooth muscle cells of vessel walls in atherosclerosis.

Deposition of *proteins*: reabsorbed proteins in kidney tubules; immunoglobulin deposits in glomeruli. Deposition of *glycogen*: in macrophages of patients with defects in lysosomal enzymes (glycogen storage diseases). Deposition of *pigments*: typically carbon, lipofuscin (breakdown product of lipid peroxidation), iron (in hemosiderosis). Pathologic calcifications:

*Dystrophic calcification*: deposition of calcium at sites of cell injury or necrosis. *Systemic calcification*: deposition of calcium in normal tissues, caused by hyperparathyroidism (consequence of parathyroid hormone excess).



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Figure 1-30 Mechanisms of cellular aging. Among the several pathways contributing to aging of cells and organisms, and their relevance to aging in humans remains an area of active investigation. IG







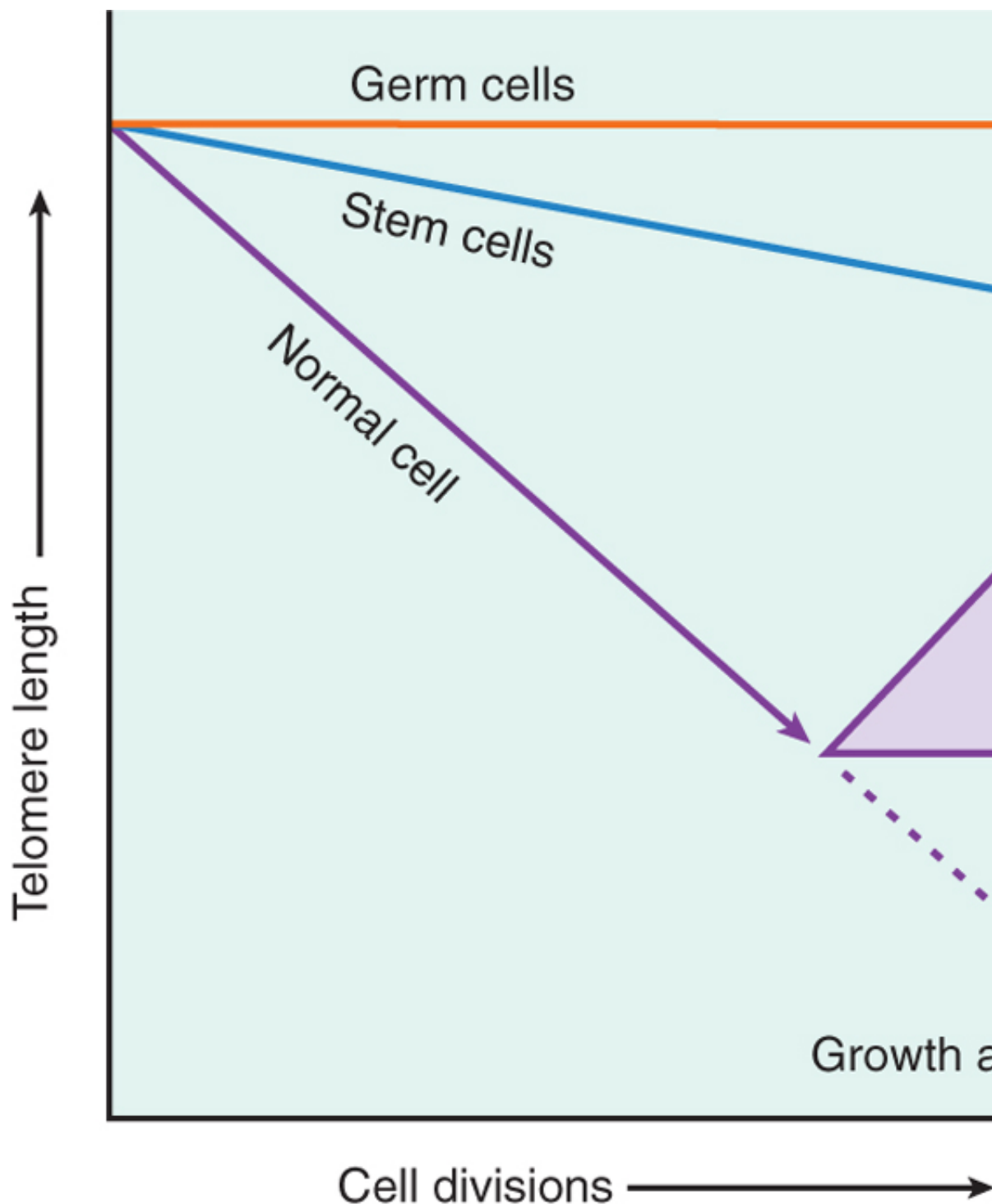
## CELLULAR AGING

*Cellular aging is the result of a progressive decline in the proliferative capacity and life span of cells due to continuous exposure to exogenous factors that cause accumulation of cellular and molecular damage.* The process of aging is conserved from yeast to humans, and—at least in simple model organisms—sees a limited number of genes. The idea that aging is controlled by particular genes has spurred enormous research into its molecular pathways and in devising ways to manipulate a process that was once considered irreversible. Mechanisms are known or suspected to be responsible for cellular aging.

**DNA damage.** Cellular aging is associated with increasing DNA damage, which may happen during replication and can be enhanced by free radicals. Although most DNA damage is repaired by repair enzymes, some persists and accumulates as cells age. Some aging syndromes are associated with defects in DNA repair mechanisms, and the life span of model animals can be increased if responses to DNA damage are enhanced or proteins that stabilize DNA are introduced. In fact, the intervention that has most effectively prolonged life span in most species is *calorie restriction*. Recently, it has been proposed that calorie restriction imposes a level of stress that activates proteins of the Sirtuin family, such as Sir2, that function as histone deacetylases. These proteins may deacetylate and thereby activate DNA repair enzymes, helping to maintain DNA; in the absence of these proteins, DNA is prone to damage. **Decreased cellular replicative capacity.** Cells have a limited capacity for replication, and after a fixed number of divisions cells become a nondividing state, known as *replicative senescence*. Aging is associated with progressive loss of cells. Cells from children have the capacity to undergo more rounds of replication than do cells from older people. In contrast, cells from patients with *Werner syndrome*, a rare disease characterized by premature aging, have a markedly reduced in vitro life span. In human cells, the mechanism of replicative senescence involves incomplete replication and progressive shortening of telomeres, which ultimately results in cell cycle arrest. **Telomeres** are short repeated sequences of DNA present at the linear ends of chromosomes, ensuring the complete replication of chromosome ends and for protecting the ends from fusion. When somatic cells replicate, a small section of the telomere is not duplicated, and telomeres are progressively shortened. As the telomeres become shorter, the ends of chromosomes can no longer be seen as broken DNA, which signals cell cycle arrest. The lengths of the telomeres are maintained by nucleotide addition mediated by an enzyme called *telomerase*. Telomerase is a specialized ribonucleoprotein that uses its own RNA as a template for adding nucleotides to the ends of chromosomes. It is highly expressed in germ cells and is present at low levels in stem cells, but it is usually absent in most somatic cells (Fig. 1-31). Therefore, as cells age their telomeres become shorter and they exit the cell cycle due to inability to generate new cells to replace damaged ones. Conversely, in immortal cancer cells, telomerase is reactivated and telomeres are not shortened, suggesting that telomere elongation might be an essential step in tumor formation. This is discussed more fully in [Chapter 6](#). Despite such evidence, however, the relationship of telomerase activity and telomere length to aging and cancer has not been fully established. **Reduced regenerative capacity of tissue stem cells.** Recent studies suggest that the p16 (CDKN2A) protein accumulates in stem cells, and they progressively lose their capacity to self-renew. p16 is a physiological inhibitor of cell cycle progression; as we discuss in [Chapter 6](#), deletion or loss of p16 are associated with cancer development. **Accumulation of metabolic damage.** Cellular aging is determined by a balance between damage resulting from metabolic events occurring within the cell and counteracting molecular responses that can repair the damage. One group of potentially damaging agents is reactive oxygen species. As we have discussed earlier in the chapter, these species can cause phosphorylation and other covalent modifications of proteins, lipids, and nucleic acids. Increased oxidative damage could result from repeated environmental exposure to such influences as ionizing radiation or a reduction of antioxidant defense mechanisms. Damaged cellular organelles accumulate as cells age and may also be the result of declining function of the proteasome, the proteolytic machine that serves to degrade abnormal and unwanted intracellular proteins. Studies in model organisms, like the worm *C. elegans*, have shown that growth factors, such as insulin-like growth factor, and intracellular signaling pathways, such as the IIS (insulin-like growth factor receptor signaling) pathway, influence lifespan.



by these hormones, tend to reduce life span. The underlying mechanisms are not fully understood, but growth factors may attenuate Sir2 responses to cellular stress and thus reduce the stability



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Figure 1-31 The role of telomeres and telomerase in replicative senescence of cells. Telomere length is plotted against the number of cell divisions. In normal somatic cells there is no telomerase activity, and telomeres progressively shorten with increasing divisions. In stem cells and germ cells, telomerase is active, and telomere length is maintained. In cancer cells, telomerase is often reactivated, and telomere length is stabilized. (Modified by permission of Elsevier Publishers Ltd, from Holt SE, et al: Refining the telomere-telomerase hypothesis of aging and cancer. Nat Biol 2001; 3: 1053-1061.)

## SUMMARY

### Cellular Aging

Results from combination of accumulating cellular damage (e.g., by free radicals, reduced capacity to divide (replicative senescence), and reduced ability to repair damaged DNA) *Accumulation of DNA damage*: defective DNA repair mechanisms; repair may be activated by calorie restriction (known to prolong aging in model organisms) *Replicative senescence*: reduced capacity of cells to divide because of decreasing amounts of telomerase and progressive shortening of chromosomes (telomeres) *Other factors*: progressive accumulation of metabolic damage; position of growth factors that promote aging in simple model organisms

It should be apparent that the various forms of cellular derangements and adaptations described in this book cover a wide spectrum, ranging from adaptations in cell size, growth, and function; to the reversible and irreversible cell injury; to the regulated type of cell death represented by apoptosis. Reference is made throughout this book because all organ injury and ultimately all clinical disease arise from derangements in structure and function.

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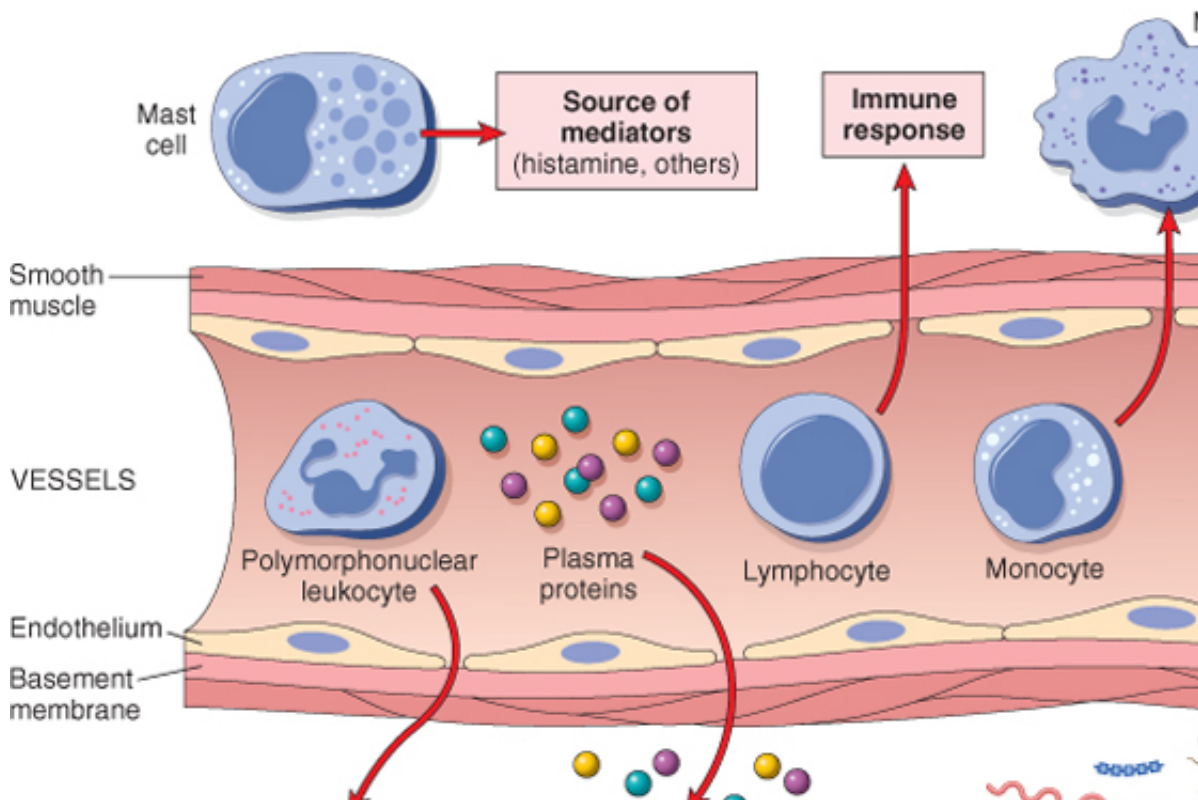
## 2 Acute and Chronic Inflammation

### OVERVIEW OF INFLAMMATION

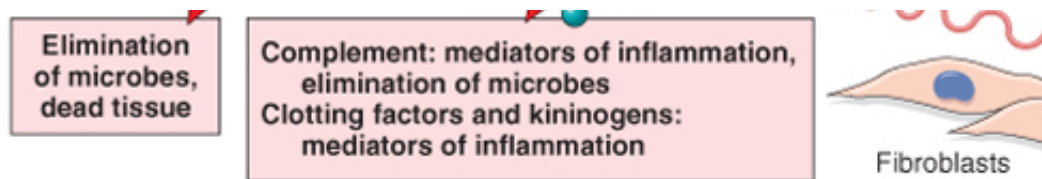
The survival of all organisms requires that they eliminate foreign invaders, such as infectious pathogens. These functions are mediated by a complex host response called *inflammation*. *Inflammation is a protective response to the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult.* The response involves diluting, destroying, or otherwise neutralizing harmful agents (e.g., microbes and toxins) and eventually heal and repair the sites of injury ([Chapter 3](#)). Without inflammation, infections would not heal. In the context of infections, inflammation is part of a broader protective response that involves the immune system ([Chapter 5](#)).

*Although inflammation helps clear infections and other noxious stimuli and initiates repair, the inflammatory response can cause considerable harm.* The components of the inflammatory reaction that destroy pathogens are capable of also injuring normal tissues. Therefore, injury may accompany entirely normal responses and the pathology may even become the dominant feature if the reaction is very strong (e.g., when the eliciting agent resists eradication), or inappropriate (e.g., when it is directed against self-antigens or against usually harmless environmental antigens in allergic disorders). Some of the most vexing clinical problems in medicine have their pathophysiologic basis in inappropriate, often chronic, inflammation. This is why the process of inflammation is a central theme in all of clinical medicine.

The cells and molecules of host defense normally circulate in the blood, and the goal of the inflammatory response is to bring them to the site of infection or tissue damage. Several types of cells and molecules play important roles in inflammation: leukocytes and plasma proteins, cells of vascular walls, and cells and extracellular matrix (ECM) components ([Figure 2-1](#)).







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Figure 2-1 The components of acute and chronic inflammatory responses and their principal functions. The roles of these components are described in this chapter.

Inflammation can be acute or chronic. Acute inflammation is rapid in onset and of short duration, lasting a few days, and is characterized by fluid and plasma protein exudation and a predominantly neutrophilic infiltrate. Chronic inflammation may be more insidious, is of longer duration (days to years), and is typified by influx of mononuclear cells, associated vascular proliferation and fibrosis (scarring). However, as we will see later, these basic patterns of inflammation have many variables that modify their course and histologic appearance.

All acute inflammatory reactions follow a fairly stereotypical sequence in which blood vessels and phagocytes are the primary responders. When a host encounters an injurious agent (e.g., a microbe) or dead cells, phagocytes that reside in the tissue or enter from the blood. At the same time, phagocytes and other host cells react to the presence of the foreign or abnormal agent by producing chemical mediators of inflammation. These mediators are also produced by the microbes or to injured tissues. Some of these mediators act on small blood vessels in the vicinity of the site of injury to cause the recruitment of circulating leukocytes to the site where the offending agent is located. The recruitment of leukocytes is also influenced by locally produced mediators, and the activated leukocytes try to remove the injurious agent and by locally produced mediators, and the activated leukocytes try to remove the injurious agent. The unfortunate side effect of the activation of leukocytes may be damage to normal host tissues.

The external manifestations of inflammation, often called its cardinal signs, result from the vascular changes. These are heat (calor), redness (rubor), and swelling (tumor). The two additional cardinal features of acute inflammation, pain (dolor) and loss of function (functio laesa), occur as consequences of mediator elaboration and leukocyte-mediated damage. When the inflammatory response is controlled by anti-inflammatory mechanisms become active, the process subsides and the host returns to a normal state. If the injurious agent cannot be quickly eliminated, the result may be chronic inflammation.

## SUMMARY

**General Features of Inflammation** Inflammation is a beneficial host response to tissue injury. It is itself capable of causing tissue damage. The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators of inflammation. The steps of the inflammatory response can be summarized in five Rs: (1) Recognition of the injurious agent, (2) Recruitment of leukocytes to the site of injury, (3) Regulation (control) of the response, and (4) Resolution (repair). If the inflammatory response is not controlled, it can lead to chronic inflammation. If the inflammatory response is controlled, it leads to the elimination of the noxious stimulus followed by decline of the damaged tissue, or persistent injury resulting in chronic inflammation.

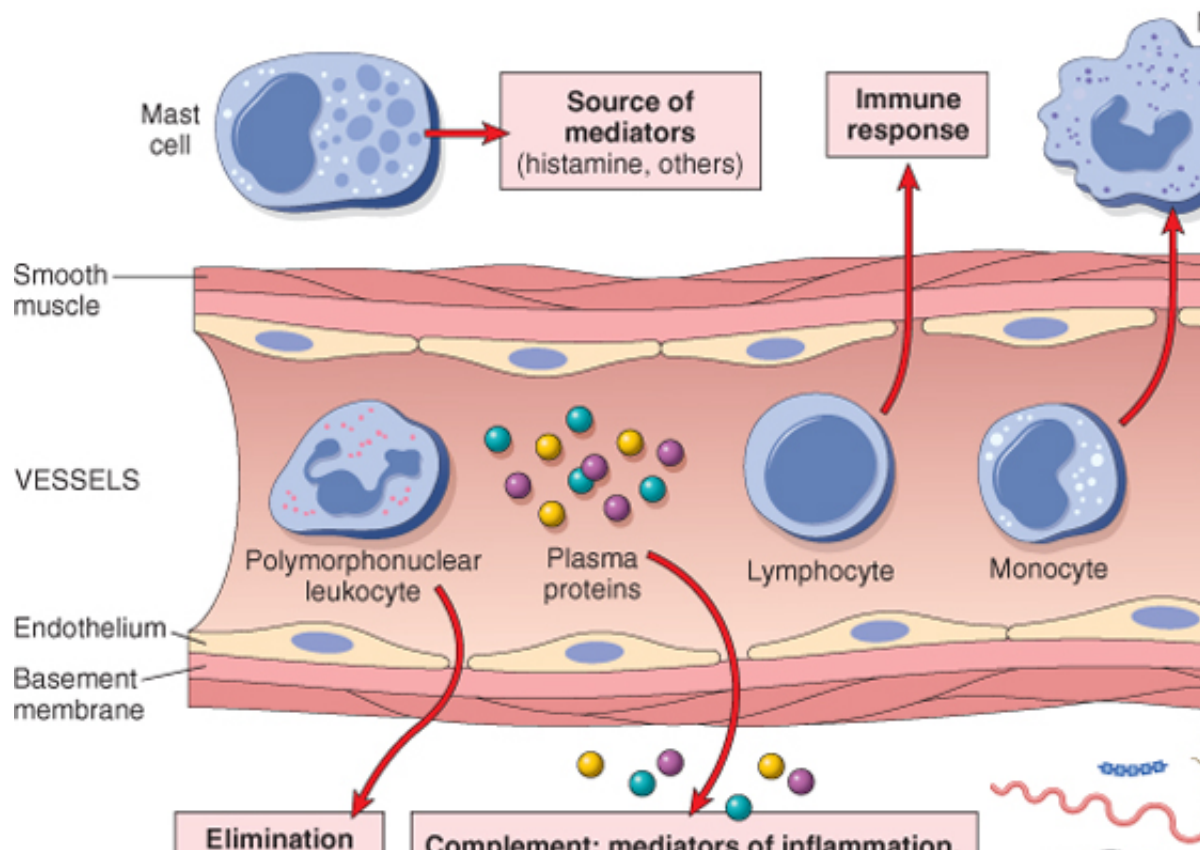


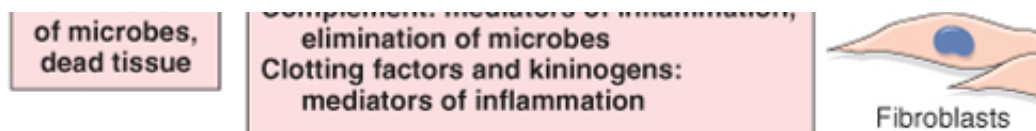
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All acute inflammatory reactions follow a fairly stereotypical sequence in which blood vessels and leukocytes are activated. When a host encounters an injurious agent (e.g., a microbe) or dead cells, phagocytes that reside in the tissue respond. At the same time, phagocytes and other host cells react to the presence of the foreign or abnormal agent by producing chemical mediators of inflammation. Mediators are also produced by the microbes or to injured tissues. Some of these mediators act on small blood vessels in the vicinity to cause vasodilation and the recruitment of circulating leukocytes to the site where the offending agent is located. The recruitment of leukocytes is mediated by locally produced mediators, and the activated leukocytes try to remove the injurious agent and by locally produced mediators, and the activated leukocytes try to remove the injurious agent. An unfortunate side effect of the activation of leukocytes may be damage to normal host tissues.

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## ACUTE INFLAMMATION

*Acute inflammation is a rapid response to injury or microbes and other foreign substances that is characterized by the leakage of plasma proteins to sites of injury.* Once there, leukocytes clear the invaders and begin the process of tissue repair.

Acute inflammation has two major components (Fig. 2-2):

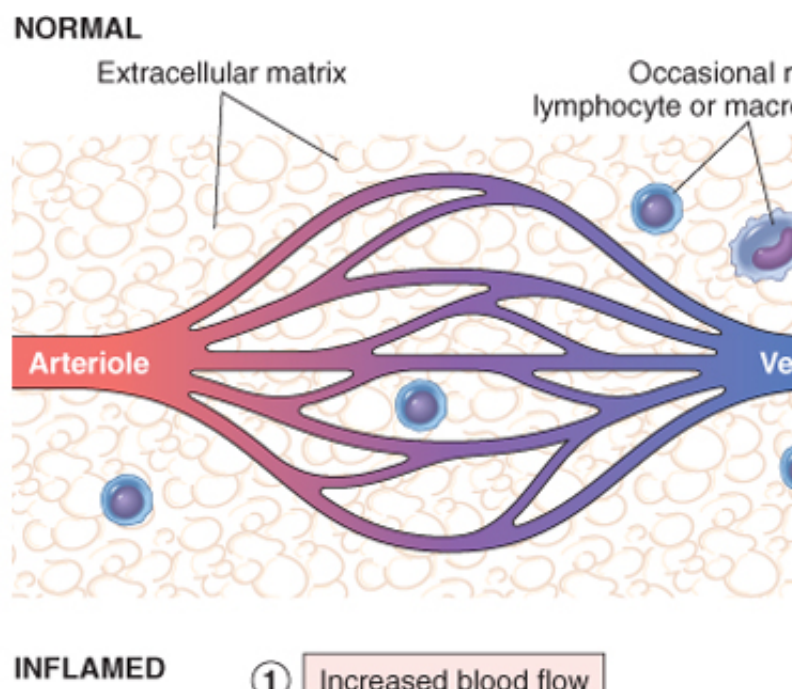
**Vascular changes:** alterations in vessel caliber resulting in increased blood flow (*vasodilation*) and increased permeability of blood vessels, allowing plasma proteins to leave the circulation (*increased vascular permeability*). **Cellular events:** increased microcirculation and accumulation in the focus of injury (*cellular recruitment and activation*). The primary cells of inflammation are neutrophils (polymorphonuclear leukocytes).

### Stimuli for Acute Inflammation

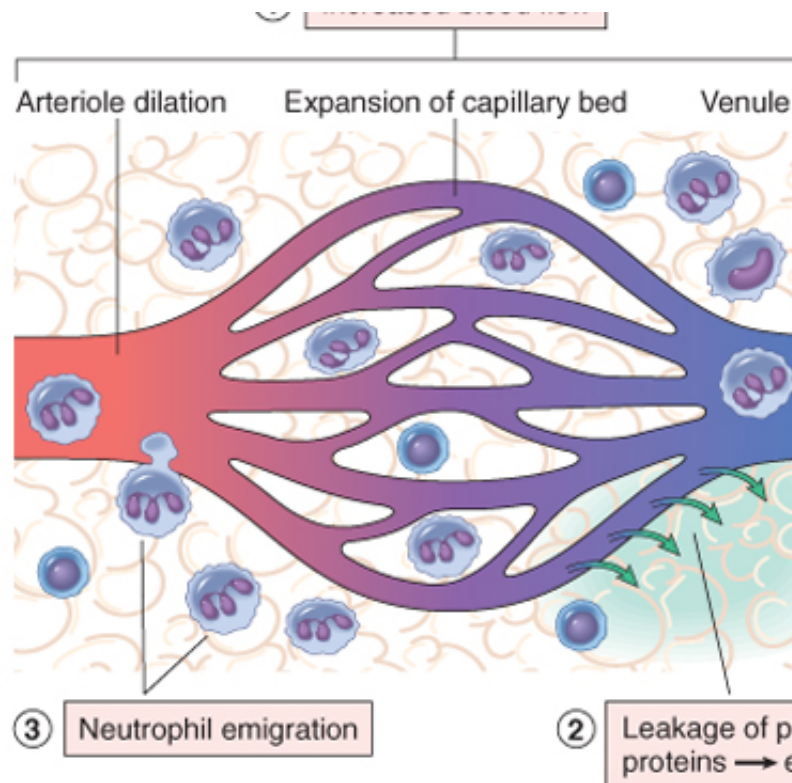
Acute inflammatory reactions may be triggered by a variety of stimuli.

**Infections** (bacterial, viral, fungal, parasitic) are among the most common and medically important causes of acute inflammation. **Physical and chemical agents** (thermal injury, e.g., burns or frostbite, and chemical agents) injure host cells and elicit inflammatory reactions. **Tissue necrosis** (from any cause, e.g., myocardial infarct) and physical and chemical injury. **Foreign bodies** (splinters, dirt, sutures) elicit inflammatory reactions against environmental substances or against self tissues. Because these responses cannot be eliminated, such reactions tend to be persistent, often have features of chronic inflammation, and are important causes of morbidity and mortality. The term "immune-mediated inflammatory disorders" is used to describe a group of disorders.

Each of these stimuli may induce reactions with some distinctive characteristics, but all inflammatory reactions share certain features. We describe first the typical reactions of acute inflammation and its morphologic features, and then the cellular and molecular mechanisms responsible for these reactions.







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 Figure 2-2 The major local manifestations of acute inflammation, compared to normal. (1) Vascular dilation and engorgement (causing warmth), (2) extravasation and deposition of plasma fluid and proteins (edema), and (3) leukocyte (mainly neutrophil) emigration (causing redness and swelling).  
 injury.

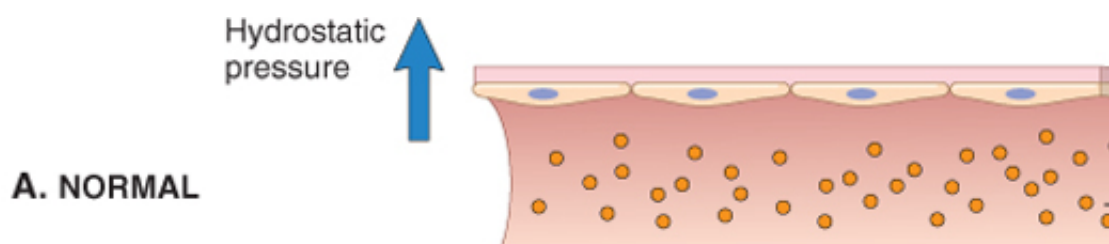
## Vascular Changes

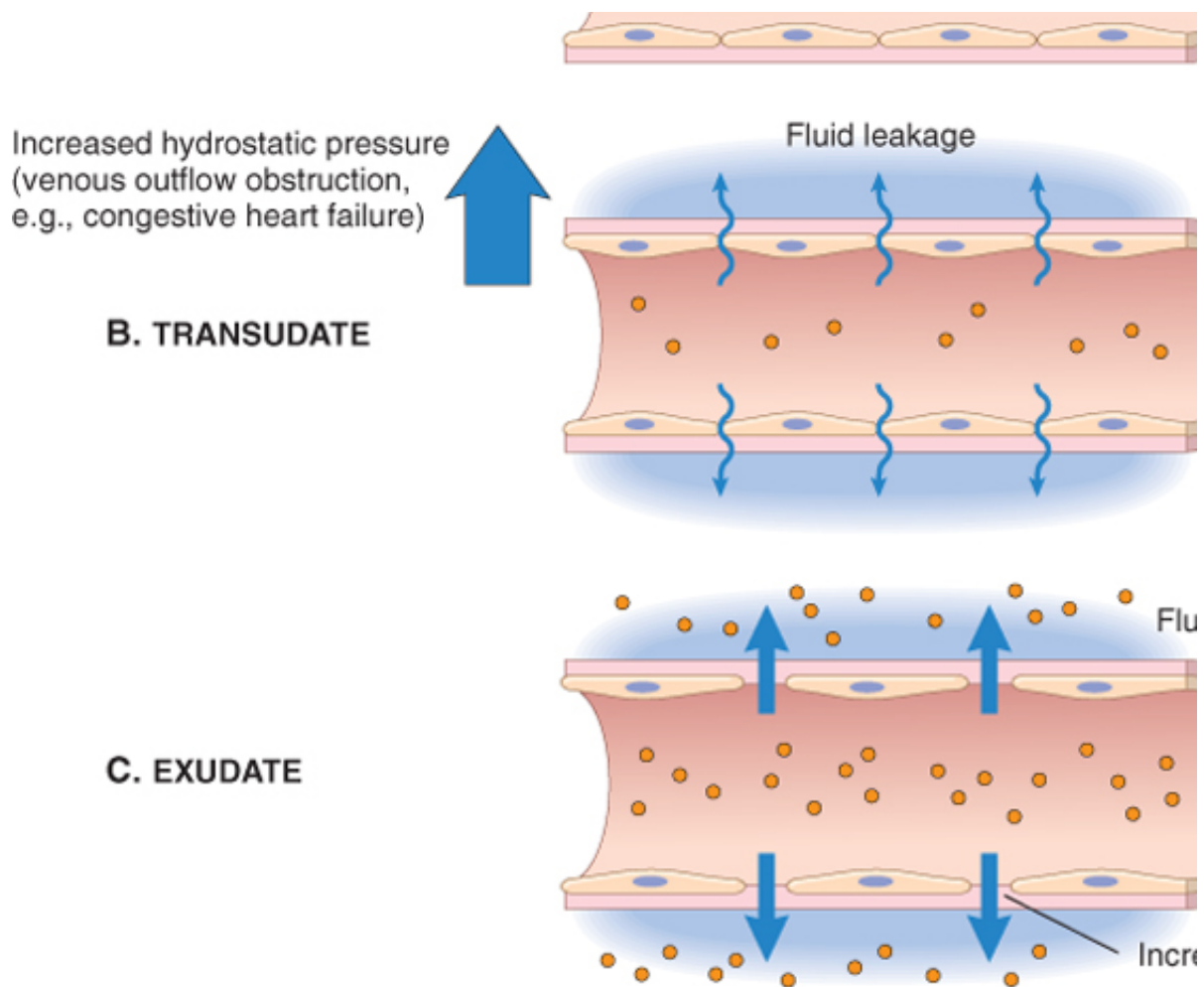
### *Changes in Vascular Caliber and Flow*

Changes in blood vessels begin rapidly after infection or injury but may develop at variable rates, depending on the intensity of the original inflammatory stimulus.

After transient vasoconstriction (lasting only for seconds), arteriolar *vasodilation* occurs, resulting in engorgement of the down-stream capillary beds (see Fig. 2-2). This vascular expansion is responsible for the warmth characteristically seen in acute inflammation. As the microvasculature becomes more congested, the red blood cells become more concentrated, slowing the circulation. These changes are reflected microscopically by numerous dilated vessels and slowly flowing blood, a process called *stasis*. As stasis develops, leukocytes (principally neutrophils) adhere to the vascular endothelial surface, a process called *margination*. This is the first step in the process of leukocyte migration from the vascular wall into the interstitial tissue (described later).

### *Increased Vascular Permeability*





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Figure 2-3 Formation of transudates and exudates. **A**, Normal hydrostatic pressure (blue arrows) is about 32 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (green arrows). Therefore, the net flow of fluid across the vascular bed is almost nil. **B**, A transudate is formed when fluid leaks or decreased osmotic pressure. **C**, An exudate is formed in inflammation because vascular permeability increases and

In the early phase of inflammation, arteriolar vasodilation and increased volume of blood flow lead to increased pressure, resulting in movement of fluid from capillaries into the tissues (Fig. 2-3). This fluid, called ultrafiltrate of blood plasma and contains little protein. However, transudation is soon eclipsed by inflammation, which allows the movement of protein-rich fluid and even cells (called an *exudate*) into the interstitium. The perivascular space reduces the intravascular osmotic pressure and increases the osmotic pressure, leading to outflow of water and ions into the extravascular tissues. Fluid accumulation in extravascular space is called transudate or exudate. Whereas exudates are typical of inflammation, transudates accumulate in non-inflammatory conditions which are mentioned in Figure 2-3 and described in more detail in Chapter 4.

Several mechanisms may contribute to increased vascular permeability in acute inflammatory reactions.

*Endothelial cell contraction leading to intercellular gaps in postcapillary venules* is the most common mechanism of increased vascular permeability. It is a reversible process elicited by histamine, bradykinin, leukotrienes, and prostaglandins. Endothelial cell contraction occurs rapidly after binding of mediators to specific receptors, and is called the *immediate transient response*. A slower and more prolonged retraction of endothelial cells, which may be induced by cytokines such as tumor necrosis factor (TNF) and interleukin-1, takes 4 to 6 hours to develop after the initial trigger and persists for 24 hours or more. *Endothelial cell injury* leading to endothelial cell necrosis and detachment. Direct injury to endothelial cells is usually

causing endothelial cell necrosis and detachment. Direct injury to endothelial cells is usual (e.g., in trauma and some infections). In most cases leakage begins immediately after the injury and persists until the damaged vessels are thrombosed or repaired. Therefore, this reaction is known as the *immediate leakage*. Capillaries, and arterioles can all be affected, depending on the site of the injury. Direct injury to capillaries causes *delayed prolonged leakage* that begins after a delay of 2 to 12 hours, lasts for several hours, and then subsides. Examples include mild to moderate thermal injury, certain bacterial toxins, and sunburn that appears the evening after a day in the sun). *Leukocyte-mediated endothelial injury* involves leukocyte accumulation along the vessel wall. As discussed later, activated leukocytes release mediators that cause endothelial injury or detachment. *Increased transcytosis* of proteins via an intracellular pathway increases permeability, especially after exposure to certain mediators such as vascular endothelial growth factor (VEGF) via channels formed by fusion of intracellular vesicles. *Leakage from new blood vessels*. As discussed later, angiogenesis involves new blood vessel formation (*angiogenesis*). These vessel sprouts remain leaky until they mature and form intercellular junctions. New endothelial cells also have increased expression of VEGF receptors, and some of the factors that induce angiogenesis (e.g., VEGF) directly induce increased transcytosis.

Although these mechanisms are separable, all of them may participate in the response to a particular injury. For example, in a burn, leakage results from chemically mediated endothelial contraction as well as from direct injury to the vessels.

### *Responses of Lymphatic Vessels*

Much of the emphasis in the discussion of inflammation is on the reactions of blood vessels, but lymphatic vessels also participate in the response. As is well known, the small amount of interstitial fluid formed normally is removed by lymphatic flow. In inflammation, lymph flow is increased and helps drain edema fluid from the extravascular space. Because the lymphatic system eventually equilibrates with extravascular fluid. In addition to fluid, leukocytes and cell debris may be transported. In inflammatory reactions, especially to microbes, the lymphatics may transport the offending agent. Inflammation of the lymphatics is called *lymphangitis*, as may the draining lymph nodes (*lymphadenitis*). Inflamed lymph nodes show hyperplasia of the lymphoid follicles and increased numbers of lymphocytes and phagocytic cells. This constellation of pathologic changes is termed reactive, or inflammatory, lymphadenitis (Chap. 10). A streak of lymphatic vessels near a skin wound is a telltale sign of an infection in the wound. This streaking follows the course of the lymphatics; it may be accompanied by painful enlargement of the draining lymph node.

## **SUMMARY**

**Vascular Reactions in Acute Inflammation** *Vasodilation* is induced by chemicals such as histamine (described later), and is the cause of erythema and stasis of blood flow. *Increased vascular permeability* is induced by histamine, kinins and other mediators that produce endothelial cell contraction, by direct or leukocyte-induced endothelial injury, and by increased transcytosis through the endothelium; increased vascular permeability allows plasma proteins to enter sites of infection or tissue damage; fluid leak through blood vessels results in edema.

## **Cellular Events: Leukocyte Recruitment and Activation**

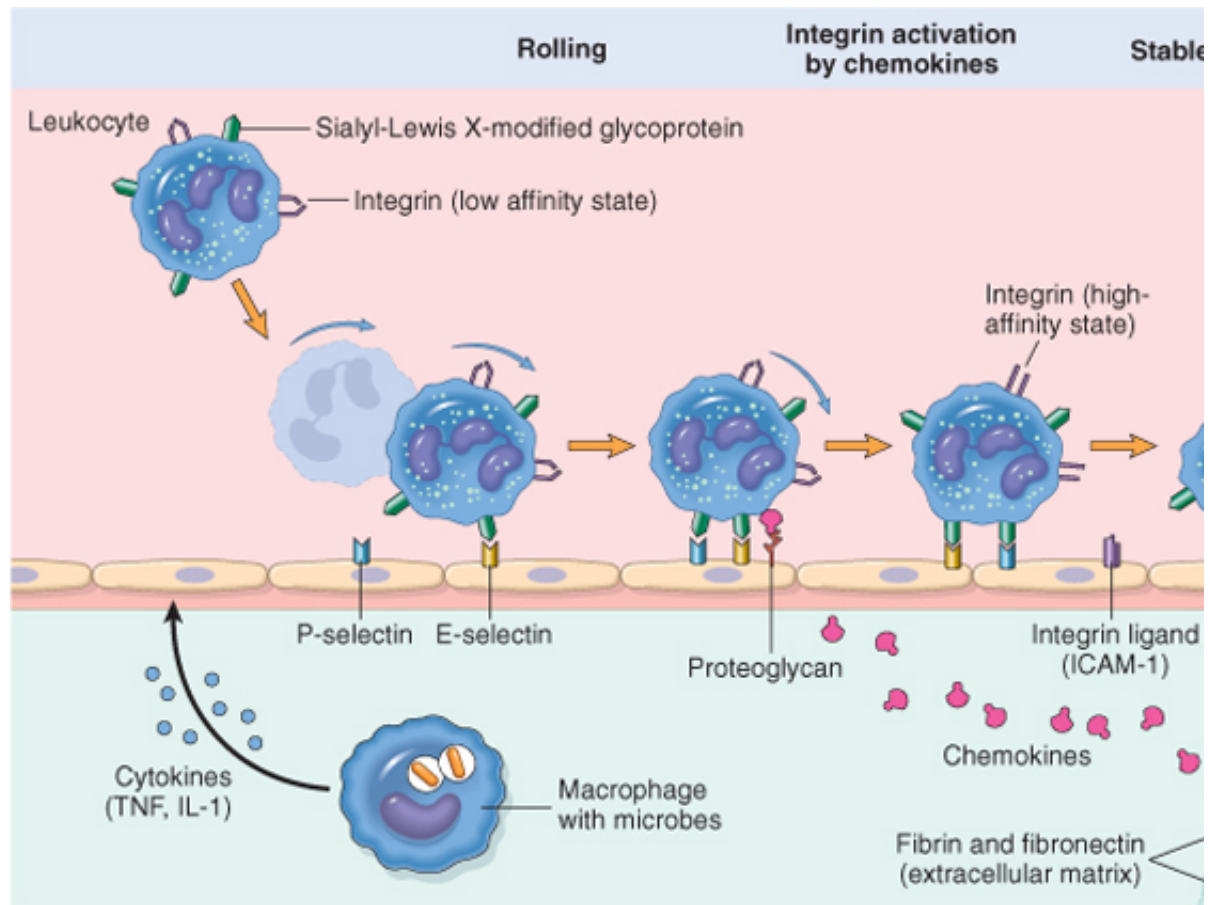
As mentioned above, an important function of the inflammatory response is to deliver leukocytes to the site of injury. Leukocytes ingest offending agents, kill bacteria and other microbes, and eliminate necrotic tissue. The major cost paid for the defensive potency of leukocytes is that, once activated, they may induce tissue damage. Leukocyte products that destroy microbes can also injure normal host tissues. Therefore, a key to effective defense is to ensure that they are recruited and activated only when needed (i.e., in response to a specific injury).

### ***Leukocyte Recruitment***

The sequence of events in the recruitment of leukocytes from the vascular lumen to the extravascular space is: (1) adhesion to endothelium, and rolling along the vessel wall; (2) firm adhesion to the endothelium; (3) migration through the endothelium; and (4) migration in interstitial tissues toward a chemotactic stimulus (Fig. 2-4). Rolling, adhesion, and migration are mediated by the binding of complementary adhesion molecules on leukocytes and endothelial surfaces (see Chap. 10). Chemoattractants and certain cytokines affect these processes by modulating the surface expression of adhesion molecules.

and by stimulating directional movement of the leukocytes.

## Margination and Rolling



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Figure 2-4 The complex process of leukocyte migration through blood vessels, shown here for neutrophils. The leukocytes adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and migrate to the source of injury. Different molecules play predominant roles in different steps of this process - selectins in rolling; proteoglycans in activating the neutrophils to increase avidity of integrins; integrins in firm adhesion; and CD31 (P-selectin binding protein 1; IL-1, interleukin 1; PECAM-1, platelet endothelial cell adhesion molecule).

As blood flows from capillaries into postcapillary venules, circulating cells are swept by laminar flow. Smaller red cells tend to move faster than the larger white cells. As a result, leukocytes are pushed toward the periphery of vessels, a process called *margination*. Subsequently, leukocytes tumble on the endothelial surface in a process called *rolling*.

The weak and transient adhesions involved in rolling are mediated by the *selectin* family of adhesion receptors expressed on leukocytes and endothelium that contain an extracellular domain that binds to carbohydrates (hence the name). The three members of this family are E-selectin (also called CD62E), expressed on endothelium and platelets; P-selectin (CD62P), expressed on endothelium and platelets; and L-selectin (CD62L), on the surface of most leukocytes. Selectins bind to sialyl-Lewis X on leukocytes that are attached to mucin-like glycoproteins on various cells. The expression of selectins is up-regulated after stimulation. The binding of leukocytes is largely restricted to endothelium at sites of infection or tissue injury (where, for example, in nonactivated endothelial cells, P-selectin is found primarily in intracellular Weibel-Palade bodies). Upon exposure to mediators such as histamine or thrombin, P-selectin is distributed to the cell surface. Similarly, E-selectin, which is not expressed on normal endothelium, is induced after stimulation by cytokines.



Similarly, E-selectin, which is not expressed on normal endothelium, is induced after stimulation by IL-1 and TNF.

## Adhesion and Transmigration

**Table 2-1. Endothelial and Leukocyte Adhesion Molecules**

Endothelial Molecule	Leukocyte Molecule	Major Role
P-selectin	Sialyl-Lewis X-modified proteins	Rolling (neutrophils, monocytes,
E-selectin	Sialyl-Lewis X-modified proteins	Rolling and adhesion (neutrophil
GlyCam-1, CD34	L-selectin	Rolling (neutrophils, monocytes)
ICAM-1 (immunoglobulin family)	CD11/CD18 integrins (LFA-1, Mac-1)	Adhesion, arrest, transmigration
VCAM-1 (immunoglobulin family)	VLA-4 integrin	Adhesion (eosinophils, monocyte
CD31	CD31	Transmigration (all leukocytes)

\*L-selectin-CD34 interactions are also involved in the "homing" of circulating lymphocytes to the high endothelial venules in lymph nodes. ICAM-1, Intercellular adhesion molecule 1; LFA-1, leukocyte function-associated antigen 1; VCAM-1, vascular cell adhesion molecule 1.

The next step in the reaction of leukocytes is firm *adhesion* to endothelial surfaces. This adhesion involves leukocyte cell surfaces interacting with their ligands on endothelial cells (see Fig. 2-4 and Table 2-1). Integrins are heterodimeric glycoproteins (composed of different  $\alpha$  and  $\beta$  chains) that also function as cell receptors. Integrins are normally expressed on leukocyte plasma membranes in a low-affinity form and do not bind to endothelial cells. When the leukocytes are activated by chemokines, chemokines are chemoattractant cytokines that are released during inflammation and are displayed bound to proteoglycans on the endothelial surface. When leukocytes encounter the displayed chemokines, the cells are activated, and their integrins undergo a conformational change, thus converting to a high-affinity form. At the same time, other cytokines, notably TNF and IL-1 (inflammation and injury), activate endothelial cells to increase their expression of ligands for integrins. These ligands include ICAM-1 (intercellular adhesion molecule 1), which binds to the integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), and VCAM-1 (vascular cell adhesion molecule 1), which binds to the integrin VLA-4 (see Table 2-1). The net result of cytokine-stimulated endothelial cells is increased expression of integrin ligands is stable attachment of leukocytes to endothelial cells at sites of inflammation.

After being arrested on the endothelial surface, leukocytes *migrate* through the vessel wall primarily through intercellular junctions (although intracellular movement through endothelial cell cytoplasm has also been observed). Leukocyte migration, called *diapedesis*, occurs mainly in the venules of the systemic vasculature; it has also been observed in pulmonary circulation. Migration of leukocytes is driven by chemokines produced in extravascular tissues. In addition, PECAM-1 (platelet endothelial cell adhesion molecule-1) expressed on leukocytes and endothelial cells, mediates the binding of leukocytes to the endothelium. After passing through the endothelium, leukocytes cross vascular basement membranes and secrete collagenases.

## Chemotaxis

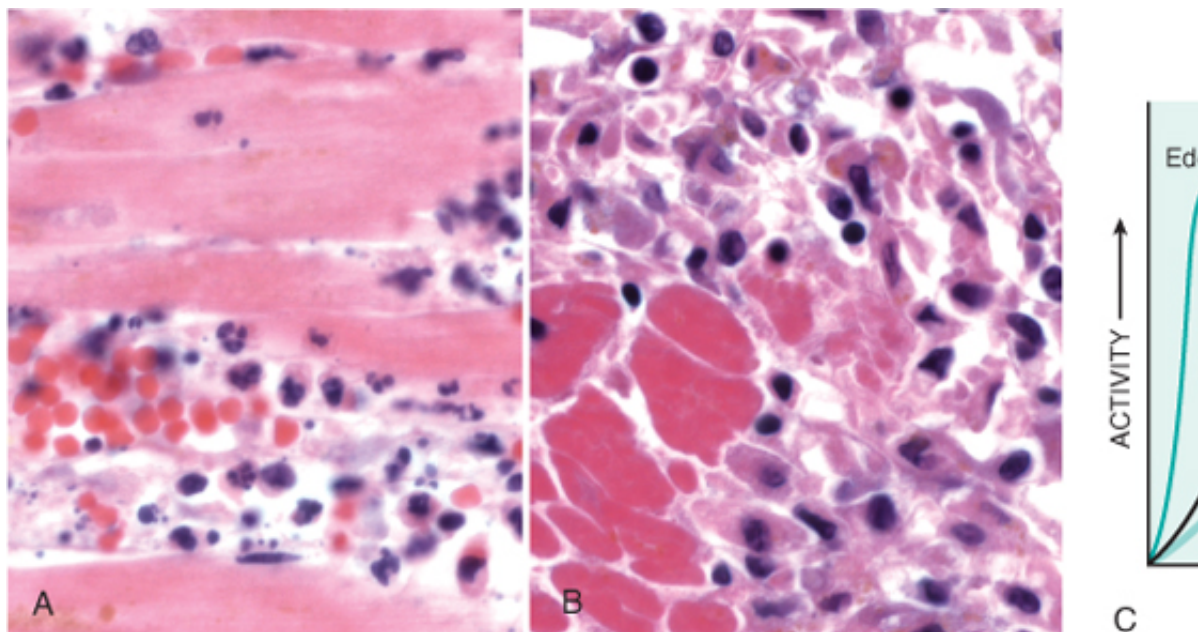
After extravasating from the blood, leukocytes migrate toward sites of infection or injury along a chemical gradient, a process called *chemotaxis*. Both exogenous and endogenous substances can be chemotactic for leukocytes, including (1) peptides with *N*-formylmethionine termini; (2) cytokines, especially those of the *chemokine* family; (3) complement system, particularly C5a; and (4) products of the lipoxygenase pathway of arachidonic acid (AA) namely LTB<sub>4</sub>. These mediators, which are described in more detail later, are produced in response to inflammatory and immunologic reactions. Leukocyte infiltration in all these situations results from the actions of various chemotactic molecules.

Chemotactic molecules bind to specific cell surface receptors, which are members of the seven-transmembrane domain (7-TM) family. Binding of the chemoattractants results in G-protein-mediated signal transduction events, leading to the release of calcium, which triggers the assembly of cytoskeletal contractile elements necessary for movement. Actin monomers are polymerized into long filaments; at the same time, actin filaments elsewhere in the cell are depolymerized in the direction of the extending pseudopod. The direction of such movement is specified by a higher order of organization of the interactions at the leading edge of the cell.

The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of inflammation, *neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours after onset of inflammation* (Fig. 2-5). Several features of leukocytes account for this sequence: neutrophils are more responsive to chemokines, and they may attach more firmly to the adhesion molecules that are rapidly expressed on endothelium and E-selectins. In addition, after entering tissues, neutrophils are short-lived—they die by apoptosis while monocytes survive longer. There are exceptions to this pattern of cellular exudation, however (e.g., in infections caused by *Pseudomonas* organisms) the cellular infiltrate is dominated by continuously recruited lymphocytes; and in some hypersensitivity reactions eosinophils may be the first cells to arrive; and in some hypersensitivity reactions eosinophils may be the first cells to arrive.

## SUMMARY

**Leukocyte Recruitment to Sites of Inflammation** Leukocytes are recruited to sites of infection or tissue injury, and are activated to perform their functions. The process is a multi-step process consisting of loose attachment to and rolling on endothelium (mediated by selectins); firm attachment to endothelium (mediated by integrins); and migration through endothelial spaces. Various cytokines promote expression of selectins and integrins on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (cell adhesion molecules), and promote directional migration of leukocytes (also chemokines); many of these cytokines are produced by macrophages and other cells responding to the pathogens or damaged tissue. Neutrophils predominate in the early inflammatory infiltrate and are later replaced by macrophages.



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Figure 2-5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrographs show an inflammatory reaction (infarction). **A**, Early (neutrophilic) infiltrates and congested blood vessels. **B**, Later (mononuclear) cellular infiltrates are approximations. For sake of simplicity, edema is shown as an acute transient response, although secondary edema can also occur.

## Leukocyte Activation

Once leukocytes have been recruited to the site of infection or tissue necrosis, they must be activated. Activation includes microbes, products of necrotic cells, and several mediators that are described later. These include different kinds of receptors that sense the presence of microbes. These include Toll-like receptors

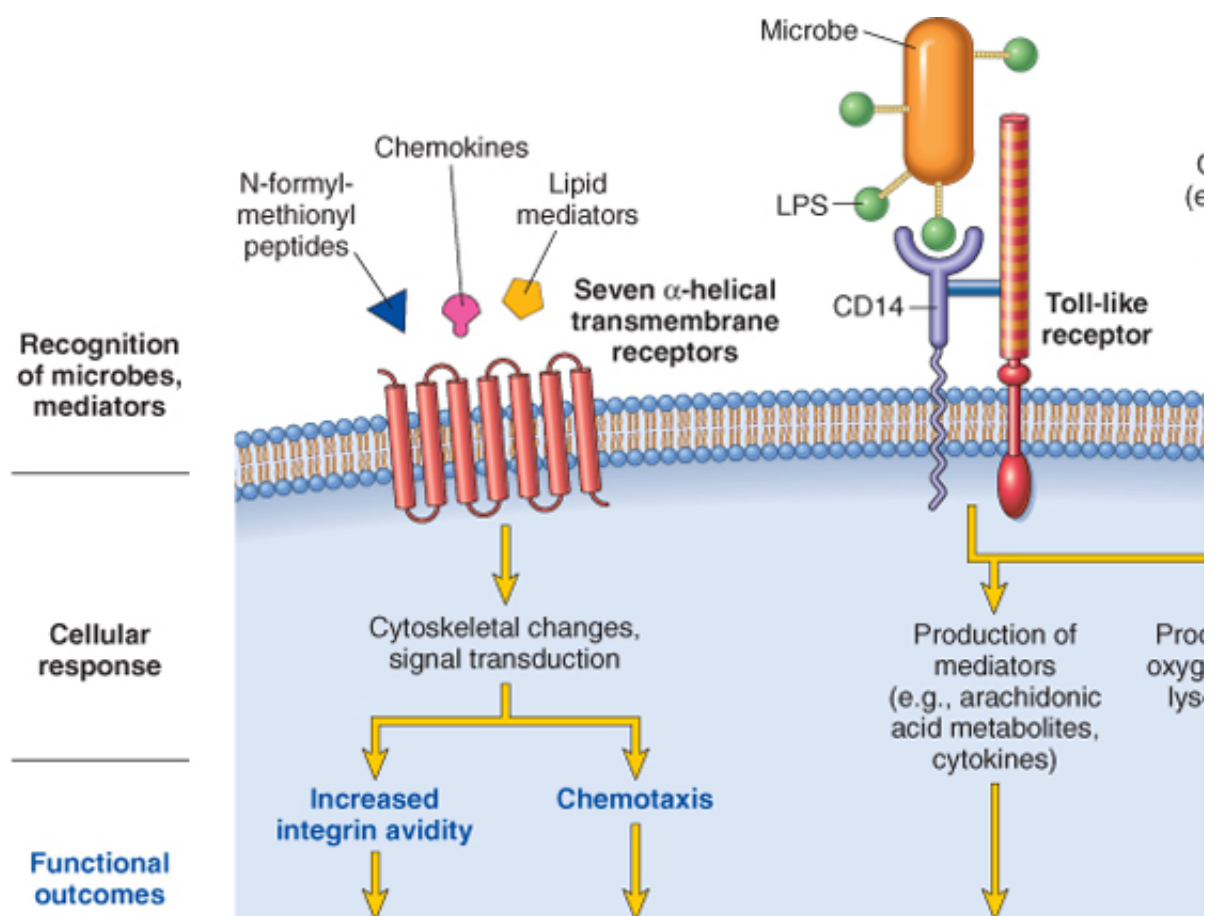
different kinds of receptors that sense the presence of microbes. These include Toll-like receptors (*Drosophila* Toll protein), which recognize endotoxin (LPS) and many other bacterial and viral products. G-protein coupled receptors, which recognize certain bacterial peptides and mediators produced in response to infection (Fig. 2-6). Engagement of these receptors by microbial products or by various mediators of inflammation in leukocytes that are part of their normal defensive functions and are grouped under the generic term *Leukocyte activation* results in many enhanced functions:

Phagocytosis of particles, an early step in the elimination of harmful substances. Production of reactive oxygen and nitrogen species. Phagocytosis of microbes and removal of dead tissues; these leukocyte products include lysosomal enzymes. Production of mediators that amplify the inflammatory reaction, including cytokines.

## Phagocytosis

Phagocytosis consists of three distinct but interrelated steps (Fig. 2-7): (1) recognition and attachment of the microbe to the leukocyte; (2) engulfment, with subsequent formation of a phagocytic vacuole; and (3) killing and digestion of the microbe.

Leukocytes bind and ingest most microorganisms and dead cells via specific surface receptors, with the help of microbes and dead cells, or host proteins, called *opsonins*, that coat microbes and target them for phagocytosis (*opsonization*). The most important opsonins are antibodies of the immunoglobulin G (IgG) class that coat microbes, breakdown products of the complement protein C3 (described below), and plasma carbohydrate that bind to microbial cell-wall sugar groups. These opsonins either are present in the blood ready to capture microbes or are produced in response to the microbes. Leukocytes express receptors for opsonins that facilitate rapid phagocytosis. These receptors include the Fc receptor for IgG (called FcγRI), complement receptors 1 and 3 (CR1 and CR3), and receptors for the collectins.



Adhesion to  
endothelium

Migration  
into tissues

Amplification of the  
inflammatory reaction

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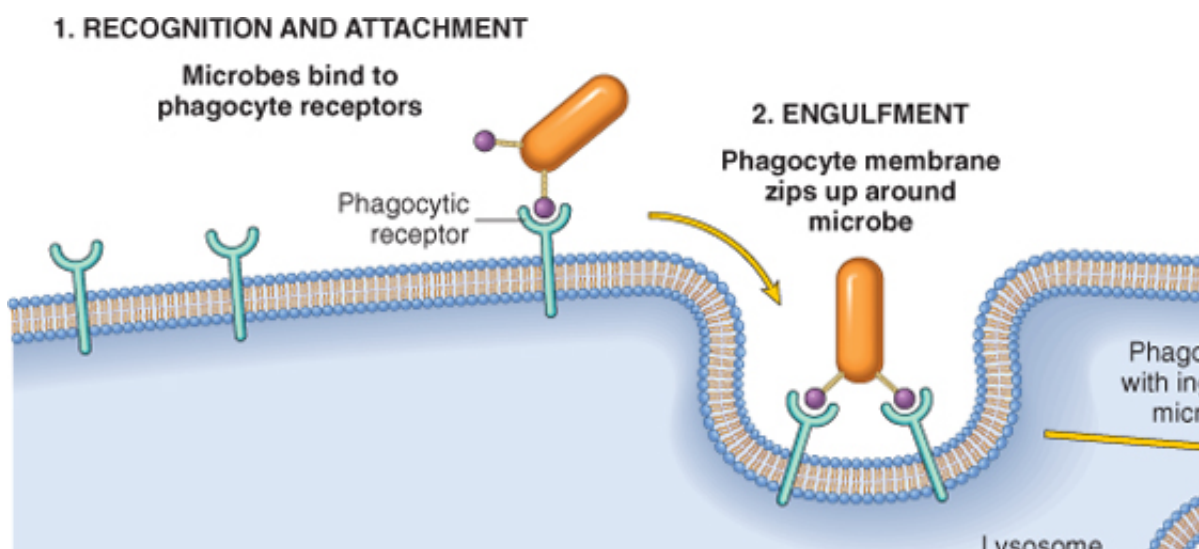
Figure 2-6 Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. functions of the leukocytes. Only some receptors are depicted (see text for details). LPS first binds to a circulating L y; LPS, lipopolysaccharide.

Binding of opsonized particles triggers *engulfment*; in addition, IgG binding to FcR and binding of induces cellular activation that enhances degradation of ingested microbes. In engulfment, pseud eventually forming a phagocytic vacuole. The membrane of the vacuole then fuses with the mem discharge of the granule's contents into the *phagolysosome*.

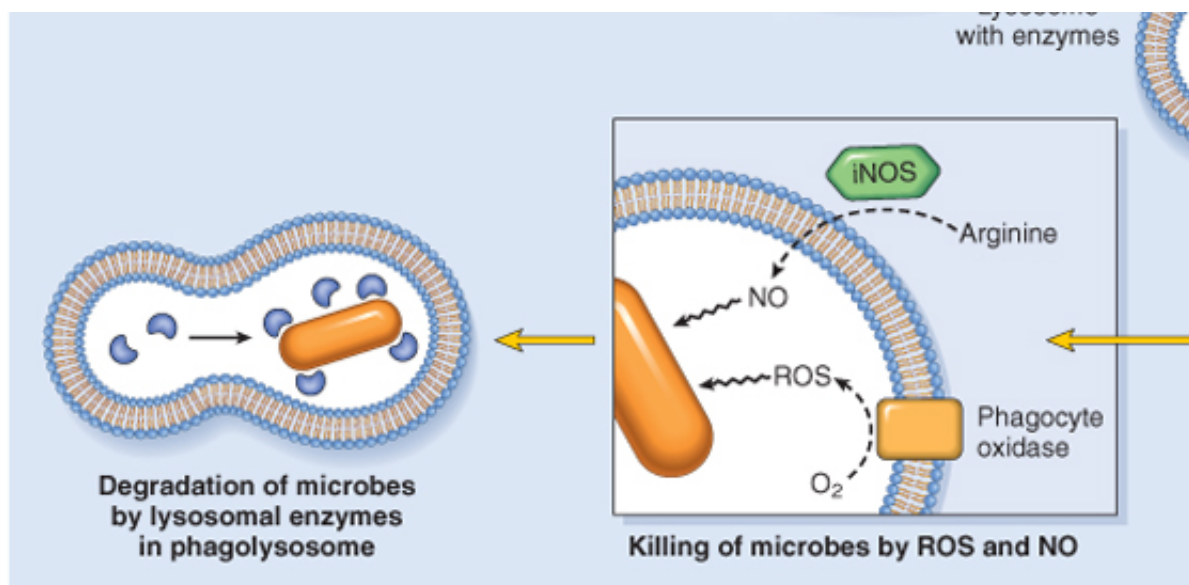
#### Killing and Degradation of Microbes

The culmination of the phagocytosis of microbes is killing and degradation of the ingested particle production of microbicidal substances within lysosomes and fusion of the lysosomes with phagosome ingested particles to the destructive mechanisms of the leukocytes. The most important microbicic species (ROS; see Fig. 2-7) and lysosomal enzymes. Phagocytosis stimulates an *oxidative burst* oxygen consumption, glycogen catabolism (glycogenolysis), increased glucose oxidation, and pi oxygen metabolites is due to rapid activation of a leukocyte NADPH oxidase, called the *phagocyte* (reduced nicotinamide adenine dinucleotide phosphate) and, in the process, converts oxygen to s ( $O_2^{\cdot -}$ ). Superoxide is then converted by spontaneous dismutation into hydrogen peroxide ( $O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2$ ). These ROS act as free radicals and destroy microbes; the mechanisms of Chapter 1. The quantities of  $H_2O_2$  produced are generally insufficient to kill most bacteria (althoug formation may be sufficient to do so). However, the lysosomes of neutrophils (called *azurophilic g* myeloperoxidase (MPO), and in the presence of a halide such as  $Cl^-$ , MPO converts  $H_2O_2$  to  $HOCl$  powerful oxidant and antimicrobial agent (NaOCl is the active ingredient in chlorine bleach) that ki and lipid peroxidation. Fortunately, the phagocyte oxidase is active only after its cytosolic subunit phagolysosome; thus, the reactive end products are generated mainly within the vesicles, and the the oxygen burst,  $H_2O_2$  is eventually broken down to water and  $O_2$  by the actions of catalase, and (Chapter 1). Reactive nitrogen species, particularly NO, act in the same way as ROS.

The dead microorganisms are then degraded by the action of lysosomal acid hydrolases. Perhaps involved in bacterial killing is elastase.







### 3. KILLING AND DEGRADATION

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Figure 2-7 Phagocytosis of a particle (e.g., a bacterium) involves (1) attachment and binding of the particle to recep fusion of the phagocytic vacuole with granules (lysosomes), and (3) destruction of the ingested particle. iNOS, In ROS, reactive oxygen species.

It is important to note that in addition to ROS and enzymes, several other constituents of leukocyte pathogens. These include *bactericidal permeability-increasing protein* (causing phospholipase act degradation), *lysozyme* (causing degradation of bacterial coat oligosaccharides), *major basic prot* constituent that is cytotoxic for parasites), and *defensins* (peptides that kill microbes by creating h

### Leukocyte-Induced Tissue Injury

Leukocytes are important causes of injury to normal cells and tissues under several circumstance

As part of a normal defense reaction against infectious microbes, when "bystander" tissues difficult to eradicate, such as tuberculosis and certain viral diseases, the host response cor the microbe itself. As a normal attempt to clear damaged and dead tissues (e.g., after a my prolong and exacerbate the injurious consequences of the infarction, especially upon repe inflammatory response is inappropriately directed against host tissues, as in certain autoim excessively against non-toxic environmental substances, such as allergic diseases that inc

In all these situations, the mechanisms by which leukocytes damage normal tissues are the same antimicrobial defense, because once the leukocytes are activated, their effector mechanisms do n During activation and phagocytosis, leukocytes may release toxic products not only within the pha space. The most important of these substances are *lysosomal enzymes*, present in the granules, *species*. In fact, if unchecked or inappropriately directed against host tissues, leukocytes themsel dependent tissue injury underlies many acute and chronic human diseases (Table 2-2), as will be disorders throughout this book.

The contents of lysosomal granules are secreted by leukocytes into the extracellular milieu by sev

If the phagocytic vacuole remains transiently open to the outside before complete closure ( *during feeding*). If cells encounter materials that cannot be easily ingested, such as immune surfaces (e.g., glomerular basement membrane), the attempt to phagocytose these substa strong leukocyte activation, and lysosomal enzymes are released into the surrounding tiss

potentially injurious substances, such as urate crystals, which damage the membrane of th

Activated leukocytes, especially macrophages, also secrete many *cytokines*, which stimulate further systemic effects, to be discussed later.

## SUMMARY

**Leukocyte Effector Mechanisms** Leukocytes can eliminate microbes and c phagocytosis, followed by their destruction in phagolysosomes. Destruction (ROS, NO) generated in activated leukocytes and lysosomal enzymes. Enzy released into the extracellular environment. The mechanisms that function to dead cells (the physiologic role of inflammation) are also capable of damagi pathologic consequences of inflammation).

## Defects in Leukocyte Function

Since leukocytes play a central role in host defense, it is not surprising that defects in leukocyte fu to increased susceptibility to infections, which may be recurrent and life-threatening (Table 2-3). T inflammation are bone marrow suppression caused by tumors and chemotherapy or radiation (res and metabolic diseases such as diabetes (causing abnormal leukocyte functions). These are desc

The genetic disorders, although individually rare, illustrate the importance of particular molecular response. Some of the better understood inherited diseases are the following:

*Defects in leukocyte adhesion.* In *leukocyte adhesion deficiency type 1 (LAD-1)*, defective leukocyte integrins LFA-1 and Mac-1 leads to impaired leukocyte adhesion to and migration phagocytosis and generation of an oxidative burst. *Leukocyte adhesion deficiency type 2* (i metabolism resulting in the absence of sialyl-Lewis X, the oligosaccharide on leukocytes th endothelium. Its clinical manifestations are similar to but milder than those of LAD-1. *Defec chronic granulomatous disease*, a genetic deficiency in one of the several components of t generating ROS. In these patients, engulfment of bacteria does not result in activation of o an attempt to control these infections, the microbes are surrounded by activated macropha that give the disease its distinctive pathology and its name. *Defects in phagolysosome form Higashi syndrome*, is an autosomal recessive disease that results from disordered intracell impairing the fusion of lysosomes with phagosomes. The secretion of lytic secretory granul affected, explaining the severe immunodeficiency seen in the disorder. Rare patients with d to carry mutations in Toll-like receptor signaling pathways.

**Table 2-2. Clinical Examples of Leukocyte-Induced Injury: Inflammatory Disor**

Disorders	Cells and Molecules Involved in Inju
<b>Acute</b>	
Acute respiratory distress syndrome	Neutrophils
Acute transplant rejection	Lymphocytes; antibodies and complement
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, mor
Septic shock	Cytokines
Vasculitis	Antibodies and complement; neutrophils
<b>Chronic</b>	
Arthritis	Lymphocytes, macrophages; antibodies
Asthma	Eosinophils, other leukocytes; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes?
Chronic transplant rejection	Lymphocytes; cytokines

Chronic transplant rejection	Lymphocytes; cytokines
Pulmonary fibrosis	Macrophages; fibroblasts

\*Listed are selected examples of diseases in which the host inflammatory response and accompanying tissue injury play a significant role in pathogenesis are discussed in much more detail in subsequent chapters.

## Outcomes of Acute Inflammation

**Table 2-3. Defects in Leukocyte Function**

Disease	Defect
<b>Acquired</b>	
Bone marrow suppression: tumors, radiation, and chemotherapy	Production of leukocytes
Thermal injury, diabetes, malignancy, sepsis, immunodeficiencies	Chemotaxis
Hemodialysis, diabetes mellitus	Adhesion
Leukemia, anemia, sepsis, diabetes, neonates, malnutrition	Phagocytosis and microbicidal activity
<b>Genetic</b>	
Leukocyte adhesion deficiency 1	$\beta$ chain of CD11/CD18 integrins
Leukocyte adhesion deficiency 2	Fucosyl transferase required for synthesis of selectins)
Chronic granulomatous disease	Decreased oxidative burst
X-linked	NADPH oxidase (membrane component)
Autosomal recessive	NADPH oxidase (cytoplasmic components)
Myeloperoxidase (MPO) deficiency	Absent MPO-H <sub>2</sub> O <sub>2</sub> system
Chédiak-Higashi syndrome	Protein involved in organelle membrane dock

Modified from Gallin JI: Disorders of phagocytic cells. In Gallin JI, et al (eds): Inflammation: Basic Principles and Clinical Correlates 861.

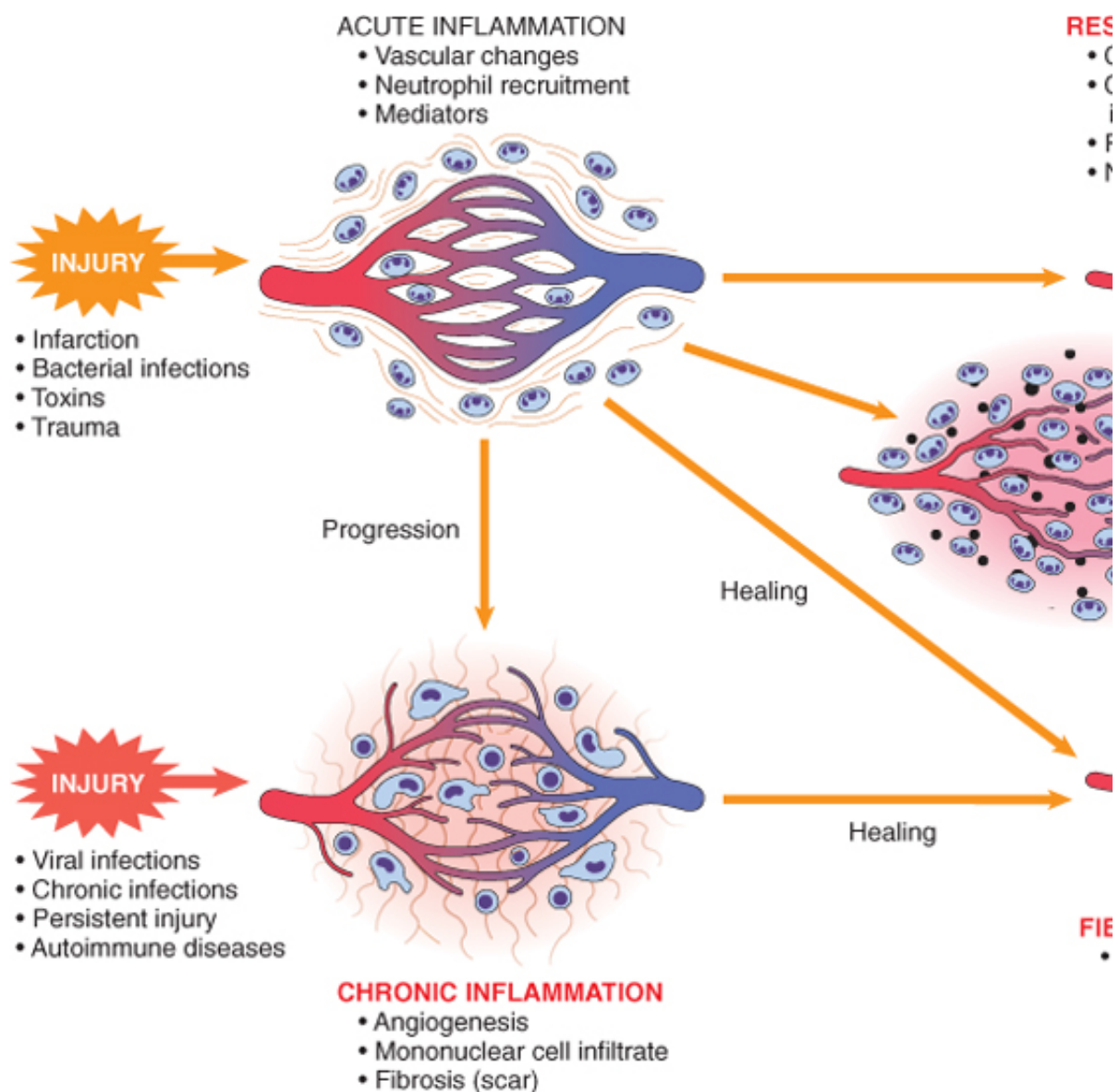
Although the consequences of acute inflammation are modified by the nature and intensity of the injury and the ability of the host to mount a response, *acute inflammation* generally has one of three outcomes:

**Resolution.** When the injury is limited or short-lived, when there has been no or minimal tissue damage, the usual outcome is restoration to normal. **Termination of the acute inflammatory response** involves neutralization, decay or enzymatic degradation of inflammatory mediators, normalization of vascular permeability, and cessation of leukocyte emigration with resolution of extravasated neutrophils. Furthermore, leukocytes begin to produce mediators that inhibit further inflammation. Eventually, the combined efforts of lymphatic drainage and macrophage ingestion of necrotic debris, edema fluid, inflammatory cells, and detritus from the battlefield (Fig. 2-9). **Progression to chronic inflammation** if the offending agent is not removed. In some instances, signs of chronic inflammation (e.g., in viral infections or immune responses to self-antigens). Depending on the extent of injury, as well as the capacity of the affected tissues to regrow, chronic inflammation may be limited to the site of injury or may lead to scarring. **Scarring or fibrosis** (Chapter 3) results after chronic inflammation occurs in tissues that do not regenerate. In addition, extensive fibrinous exudate (e.g., in severe inflammation) may not be completely absorbed and are *organized* by ingrowth of connective tissue. **Abscesses** may form in the setting of extensive neutrophilic infiltrates (see later) or in certain tissues. In some organisms are then said to be *pyogenic*, or "pus forming"). Because of the underlying tissue damage and the *usual outcome of abscess formation is scarring*.

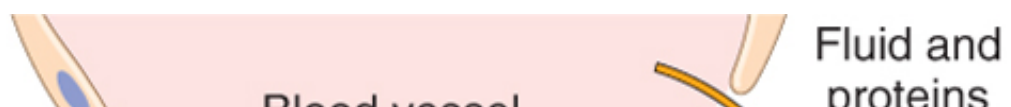
## SUMMARY

**Sequence of Events in Acute Inflammation** The vascular changes in acute inflammation are characterized by increased blood flow secondary to arteriolar and capillary dilation (hyperemia). Increased vascular permeability, either through widened interendothelial spaces or through the formation of microvascular leaks, results in the extravasation of fluid and proteins into the tissue space. This process is mediated by the release of inflammatory mediators, which act on the endothelium to increase permeability. The resulting edema and increased vascular permeability, either through widened interendothelial spaces or through the formation of microvascular leaks, results in the extravasation of fluid and proteins into the tissue space. This process is mediated by the release of inflammatory mediators, which act on the endothelium to increase permeability.

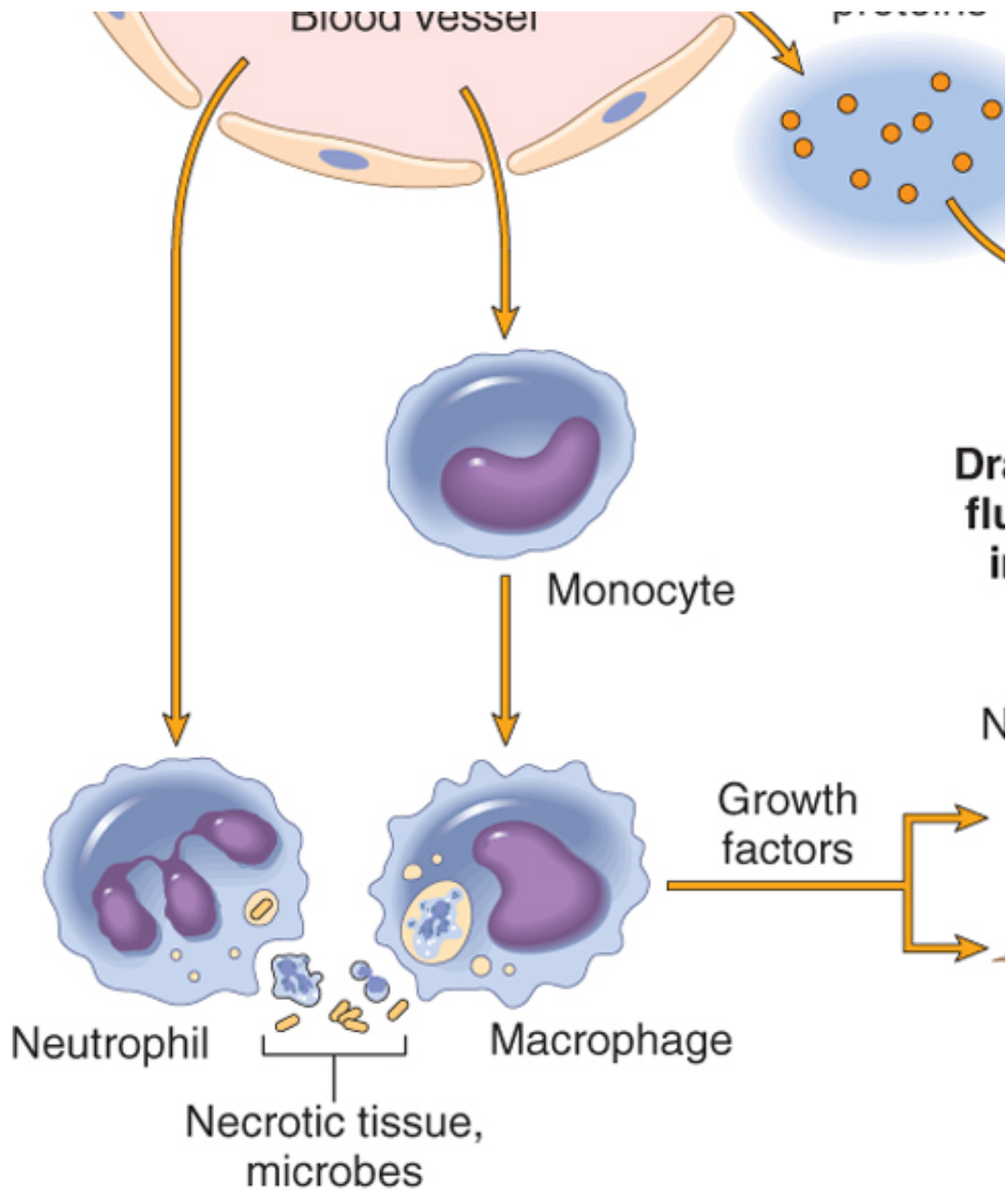
venues or by direct endothelial cell injury, results in an exudate or protein-rich (tissue edema). The leukocytes, initially predominantly neutrophils, adhere to adhesion molecules, then leave the microvasculature and migrate to the site of injury under the influence of chemotactic agents. Phagocytosis, killing, and degradation of the injurious agent follow. Genetic or acquired defects in leukocyte functions give rise to recurrent acute inflammation. Outcomes of acute inflammation may be removal of the exudate with restoration of normal tissue (resolution); transition to chronic inflammation; or extensive destruction of tissue with scarring.



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Figure 2-8 Outcomes of acute inflammation: resolution, healing by scarring (fibrosis), or chro







## Phagocytosis and clearance of necrotic tissue, microbes

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 Figure 2-9 Events in the resolution of inflammation. Phagocytes clear the fluid, leukocytes and dead tissue, and drainage. (Modified from Haslett C, Henson PM: In Clark R, Henson PM [eds]: The Molecular and Cellular Biology of Inflammation. 1996. With kind permission of Springer Science and Business Media)





## MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

The vascular and cellular reactions that characterize acute inflammation are reflected in the morphology. The severity of the inflammatory response, its specific cause, and the particular tissue involved can all influence the morphology of inflammation, producing distinctive appearances. The importance of recognizing these morphologic patterns is emphasized by the association of different eliciting stimuli and clinical situations.

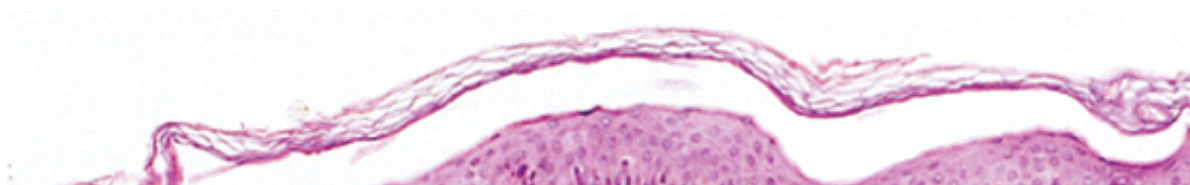
### Morphology

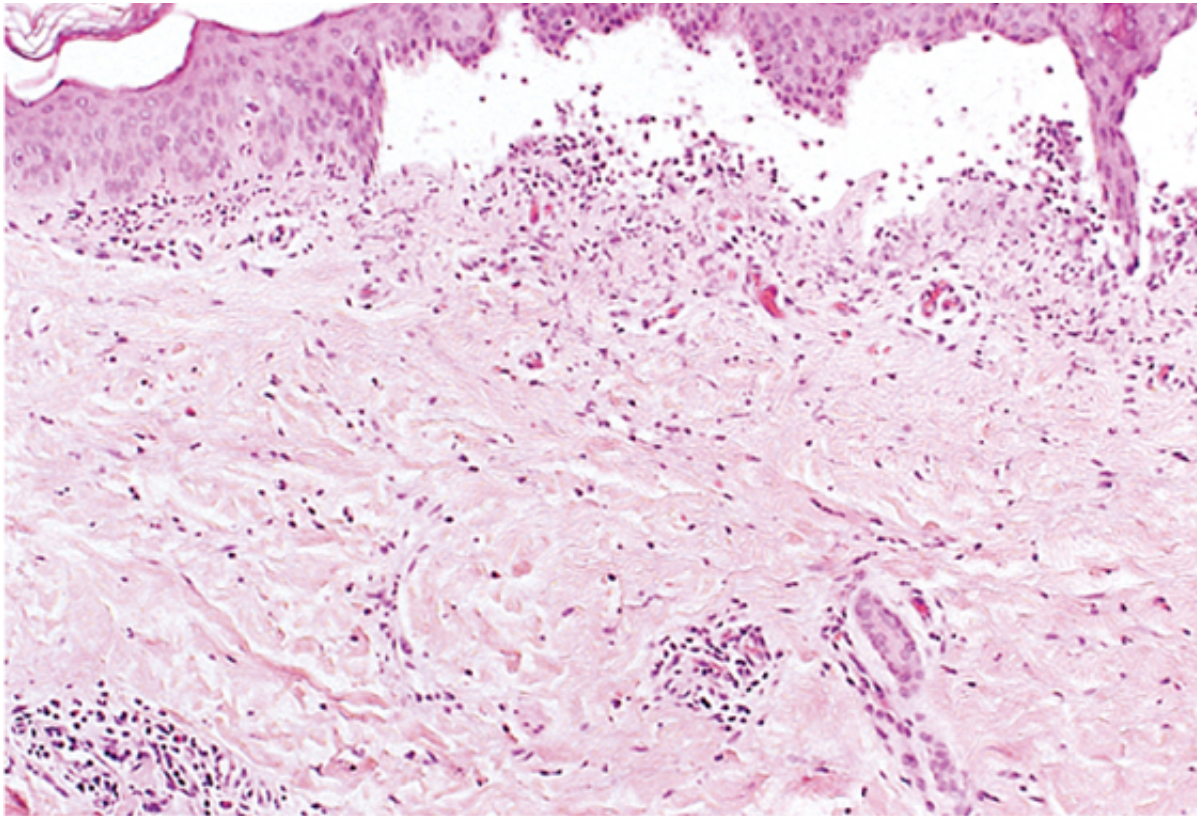
**Serous inflammation** is characterized by the outpouring of a watery, relatively protein-rich fluid. The fluid, depending on the site of injury, derives either from the serum or from the secretion of serous glands into the peritoneal, pleural, and pericardial cavities. The skin blister resulting from a burn is a good example of a serous effusion accumulated either within or immediately beneath the epidermis (Fig. 2-10). Fluid in a serous cavity is called an **effusion**.

**Fibrinous inflammation** occurs as a consequence of more severe injuries, resulting in increased vascular permeability that allows large molecules (such as fibrinogen) to pass the endothelial barrier. The accumulated extravascular fibrin appears as an eosinophilic meshwork of threads. A fibrinous exudate is characteristic of inflammatory cavities, such as the meninges, pericardium, and pleura. Such exudates may be dissolved and the accumulated debris may be removed by macrophages, resulting in restoration of normal tissue structure (**resolution**). However, failure to completely remove the fibrin results in thickening of the tissue and blood vessels (**organization**), leading ultimately to scarring that may have significant consequences. For example, organization of a fibrinous pericardial exudate forms adhesions that bridges or obliterates the pericardial space and restricts myocardial function.

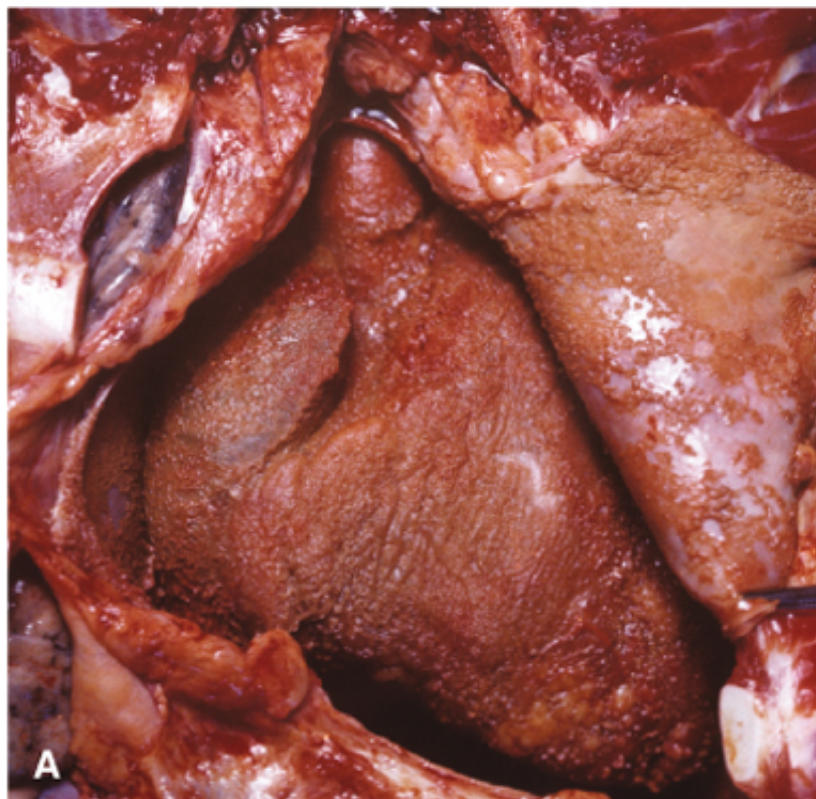
**Suppurative (purulent) inflammation** is manifested by the presence of large amounts of pus (pus) consisting of neutrophils, necrotic cells, and edema fluid. Certain organisms are more likely to induce such localized suppuration and are therefore referred to as pyogenic. Pyogenic focal collections of pus that may be caused by seeding of pyogenic organisms into tissues are called abscesses. Abscesses typically have a central, largely necrotic region surrounded by a ring of preserved neutrophils (Fig. 2-12), with a surrounding zone of dilated vessels and fibrin indicative of early repair. As time passes the abscess may become completely wall-off and eventually replaced by connective tissue.

An **ulcer** is a local defect, or excavation, of the surface of an organ or tissue that is the result of tissue necrosis and sloughing (shedding) of inflammatory necrotic tissue (Fig. 2-13). Ulcerative inflammation exists on or near a surface. It is most commonly seen in the form of inflammatory necrosis of the mucosa of the mouth, stomach, intestines, or genitourinary tract. Ulcerations are best exemplified by the peptic ulcer of the stomach or duodenum, in which acute and chronic inflammation coexist. During the healing process, intense polymorphonuclear infiltration and vascular dilation in the margins of the defect occur. At the margins and base of the ulcer develop scarring with accumulation of lymphocytes, fibroblasts, and collagen.

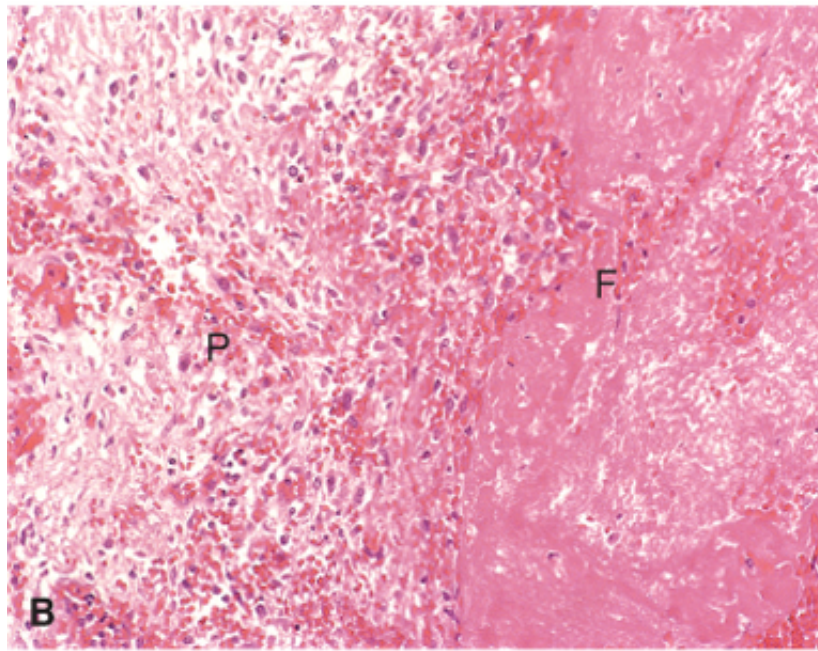




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Figure 2-10 Serous inflammation. Low-power view of a cross-section of a skin blister showing the epidermis separated by serous effusion.







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 Figure 2-11 Fibrinous pericarditis. **A**, Deposits of fibrin on the pericardium. **B**, A pink meshwork of fibrin exudate.



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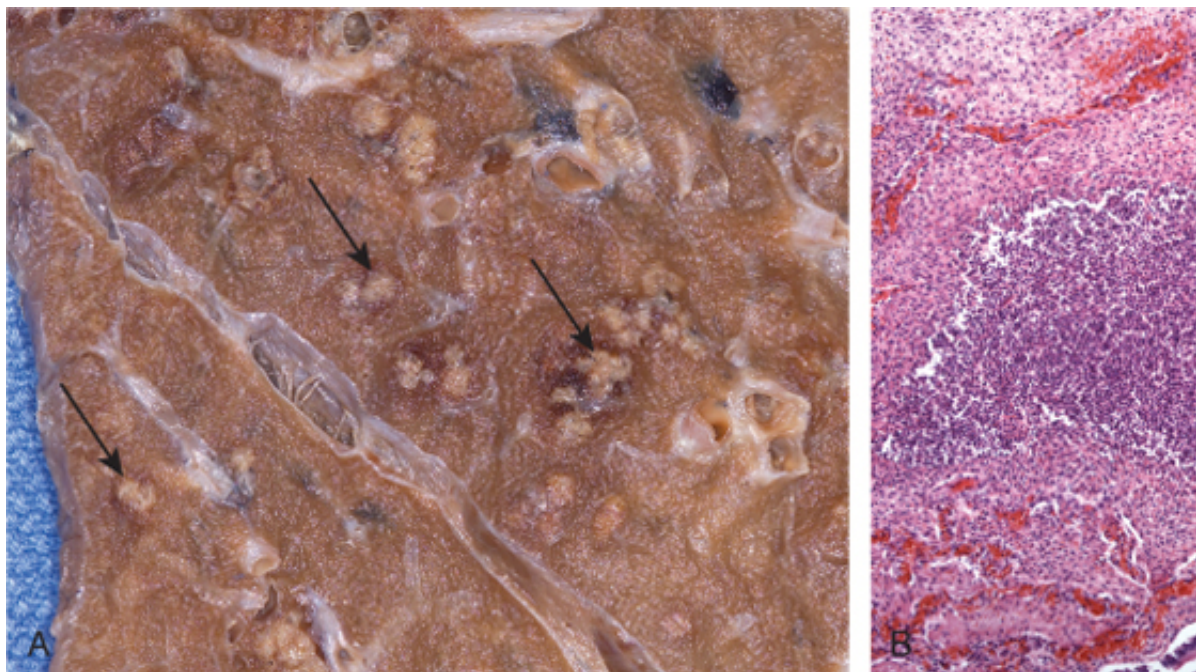




## CHEMICAL MEDIATORS OF INFLAMMATION

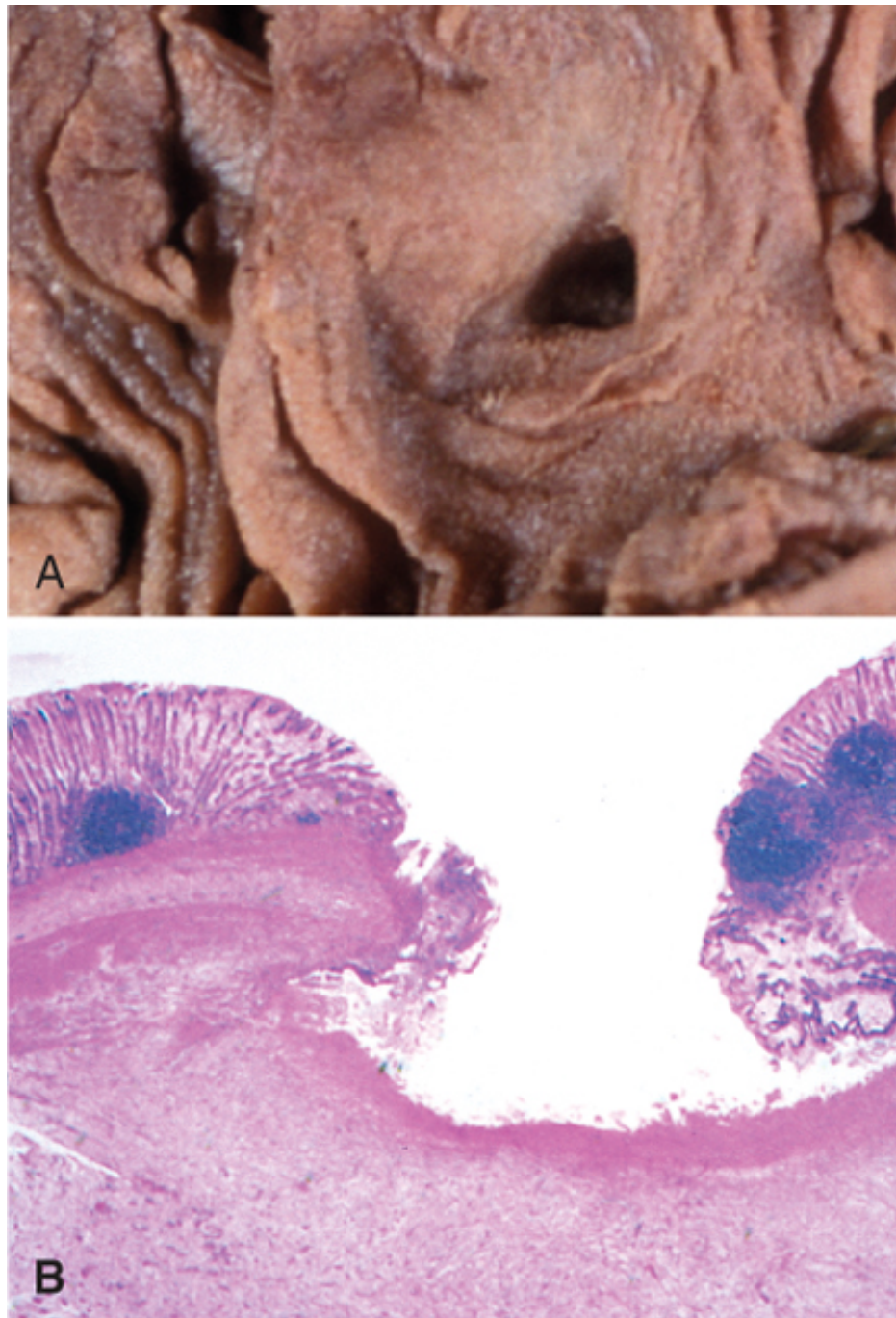
Having described the vascular and cellular events in acute inflammation, and the accompanying responses, we now describe the chemical mediators that are responsible for these events. Many mediators are known, and we will design a large armamentarium of anti-inflammatory drugs, which are prominent on our pharmacy shelves. We will emphasize general properties of the mediators of inflammation and highlight only some of the more important ones.

*Mediators may be produced locally by cells at the site of inflammation, or they may be synthesized by the liver) as inactive precursors that are activated at the site of inflammation. Some mediators are normally sequestered in intracellular granules and are rapidly secreted upon stimulation (e.g., histamine from mast cells) or are synthesized de novo in response to a stimulus (e.g., prostaglandins and leukotrienes). Mediators (complement proteins, kinins) typically undergo proteolytic cleavage to acquire their active form. Mediators induce their effects by binding to specific receptors on target cells. Mediators may act on one or more cell types, have widespread actions, with differing outcomes depending on which cell type they affect, and/or have toxic activities (e.g., lysosomal proteases and ROS). Mediators may stimulate target cells to produce other mediators. Different mediators may have similar actions, in which case they may amplify a response. The actions of most mediators are transient. Some mediators, when released from the cell, quickly decay (e.g., arachidonic acid metabolites), are inactivated (e.g., bradykinin), are eliminated (e.g., antioxidants scavenge toxic oxygen metabolites), or are neutralized by inhibitory proteins).*



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Figure 2-12 Purulent inflammation. **A**, Multiple bacterial abscesses in the lung (arrows) in a case of bronchopneumonia. The abscesses are filled with purulent exudate (cellular debris, and is surrounded by congested blood vessels).



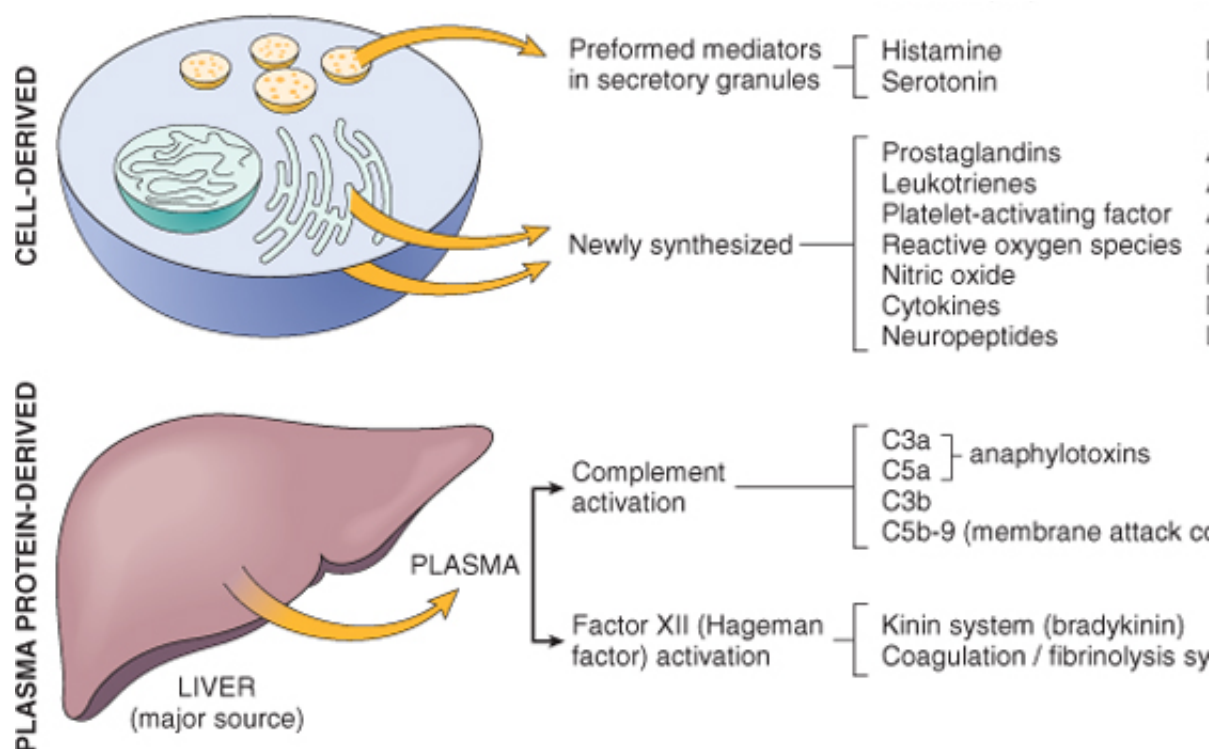


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 Figure 2-13 The morphology of an ulcer. **A**, A chronic duodenal ulcer. **B**, Low-power cross-section of a duodenal u  
 the base.

### Cell-Derived Mediators

Tissue macrophages, mast cells, and endothelial cells at the site of inflammation, as well as leuko  
 the blood, are all capable of producing different mediators of inflammation.

### *Vasoactive Amines*



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Figure 2-14 The principal chemical mediators of inflammation. EC, Endothelial cell.

The two vasoactive amines histamine and serotonin are stored as preformed molecules in mast cells and platelets, the first mediators to be released in acute inflammatory reactions. *Histamine* is produced by many cell types, as well as circulating basophils and platelets. Preformed histamine is released from mast cells in response to stimuli: (1) physical injury such as trauma or heat; (2) immune reactions involving binding of IgE to antigen (Chapter 5); (3) C3a and C5a fragments of complement, the so-called *anaphylatoxins* (see later); (4) certain proteins; (5) neuropeptides (e.g., substance P); and (6) certain cytokines (e.g., IL-1 and IL-8). In addition, histamine is the principal mediator of the immediate phase of increased vascular permeability, increased vasodilation, and increased interendothelial gaps. Soon after its release, histamine is inactivated by histaminase.

**Table 2-4. The Actions of the Principal Mediators of Inflammation**

Mediator	Source	Principal Actions
<b>Cell-Derived</b>		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability
Serotonin	Platelets	Vasodilation, increased vascular permeability
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis
Platelet-activating factor	Leukocytes, endothelial cells	Vasodilation, increased vascular permeability, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide <sub>Px</sub>	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (e.g. TNF, IL-1)	Macrophages, lymphocytes, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules); in severe infections, septic shock
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
<b>Plasma Protein-Derived</b>		



Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, opsonification
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, Interleukin-1; TNF, tumor necrosis factor.

**Serotonin** (5-hydroxytryptamine) is also a preformed vasoactive mediator, with effects similar to those of histamine. It is stored within platelet dense body granules (along with histamine, **adenosine diphosphate**, and calcium) and released during aggregation ([Chapter 4](#)).

#### *Arachidonic Acid (AA) Metabolites: Prostaglandins, Leukotrienes, and Lipoxins*

Products derived from the metabolism of AA affect a variety of biologic processes, including inflammation. **Eicosanoids** (also called *eicosanoids*) can mediate virtually every step of inflammation ([Table 2-5](#)); their synthesis, regulation, and agents that inhibit their synthesis also diminish inflammation. They can be thought of as being generated locally at the site of generation and then decay spontaneously or are enzymatically destroyed. Leukocytes and platelets are the major sources of AA metabolites in inflammation.

AA is a 20-carbon polyunsaturated fatty acid (with four double bonds) derived primarily from diet. It is released from cell membranes mainly in its esterified form as a component of cell membrane phospholipids. It is released from membranes by phospholipases that have been activated by mechanical, chemical, or physical stimuli, or by inflammatory mediators. Once released, metabolism proceeds along one of two major enzymatic pathways: *Cyclooxygenase* stimulates the synthesis of *prostaglandins* and *thromboxanes*, and *lipoxygenase* is responsible for production of *leukotrienes* and *lipoxins* ([Fig. 2-1](#)).

**Cyclooxygenase pathway.** Products of this pathway include prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), and thromboxane A<sub>2</sub> (TXA<sub>2</sub>), each derived by the action of a specific enzyme on an intermediate. PGE<sub>2</sub> has a restricted tissue distribution. For example, platelets contain the enzyme thromboxane synthase, which produces TXA<sub>2</sub>, an aggregating agent and vasoconstrictor, is the major PG produced in these cells. Endothelial cells contain thromboxane synthase but contain prostacyclin synthase, which is responsible for the formation of PGI<sub>2</sub>, a potent inhibitor of platelet aggregation. The opposing roles of TXA<sub>2</sub> and PGI<sub>2</sub> in hemostasis are fundamental. PGE<sub>2</sub> is the major metabolite of the cyclooxygenase pathway in mast cells; along with PGE<sub>2</sub> and PGI<sub>2</sub>, it causes vasodilation and potentiates edema formation. The PGs are also involved in the regulation of inflammation; PGE<sub>2</sub> augments pain sensitivity to a variety of other stimuli and interacts with other mediators of inflammation. **5-Lipoxygenase** is the predominant AA-metabolizing enzyme in neutrophils. The product, 5-hydroperoxyeicosatetraenoic acid, is quite unstable and is either reduced to 5-HETE (5-hydroxyeicosatetraenoic acid, chemotactic for neutrophils) or converted into a family of compounds collectively called *leukotrienes*. The first leukotriene generated from 5-HPETE is called *leukotriene A<sub>4</sub>* (LTA<sub>4</sub>), which in turn gives rise to LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are produced mainly in mast cells and cause vasoconstriction, bronchospasm, and edema. **Lipoxins function mainly as inhibitors of inflammation.** Once leukocytes enter tissues, they convert lipoxygenase-derived AA products to lipoxins, which inhibit neutrophil chemotaxis and adhesion. Platelets that are activated and adhere to leukocytes release lipoxins. Platelets alone cannot synthesize lipoxins A<sub>4</sub> and B<sub>4</sub> (LXA<sub>4</sub> and LXB<sub>4</sub>), but they can synthesize an intermediate derived from adjacent neutrophils, by a transcellular biosynthetic pathway. By this pathway, lipoxins are transferred from one cell to the other.

**Table 2-5. Principal Inflammatory Actions of Arachidonic Acid Metabolites (Eicosanoids)**

Action	Eicosanoid
Vasodilation	PGI <sub>2</sub> (prostacyclin), PGE <sub>1</sub> , PGE <sub>2</sub> , PGD <sub>2</sub>
Vasoconstriction	Thromboxane A <sub>2</sub> , leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub>



Increased vascular permeability	Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub>
Chemotaxis, leukocyte adhesion	Leukotriene B <sub>4</sub>

The central role of eicosanoids in inflammatory processes is emphasized by the clinical utility of a **Aspirin<sup>®</sup>** and most nonsteroidal anti-inflammatory drugs (NSAIDs), such as **ibuprofen<sup>®</sup>**, inhibit cyclooxygenase synthesis (hence their efficacy in treating pain and fever). There are two forms of the cyclooxygenase COX-1 (but not COX-2) is expressed in the gastric mucosa, and the mucosal PGs generated by COX-1 are important for gastric mucosal defense. Thus, inhibition of cyclooxygenases by **aspirin<sup>®</sup>** and other nonsteroidal anti-inflammatory drugs (NSAIDs) predisposes to gastric ulceration. To preserve the anti-inflammatory effects of cyclooxygenase effects on gastric mucosa, highly selective COX-2 inhibitors are now available. However, recent studies have shown that they have their own problems. They seem to affect PGI<sub>2</sub> synthesis more than TXA<sub>2</sub> production and hence may increase the risk of thrombosis. This can lead to a greater incidence of acute coronary artery disease. Glucocorticoids, which are part of the inflammatory response, act in part by inhibiting the activity of phospholipase A<sub>2</sub> and thus inhibiting the release of AA from membrane phospholipids.

### Platelet-Activating Factor

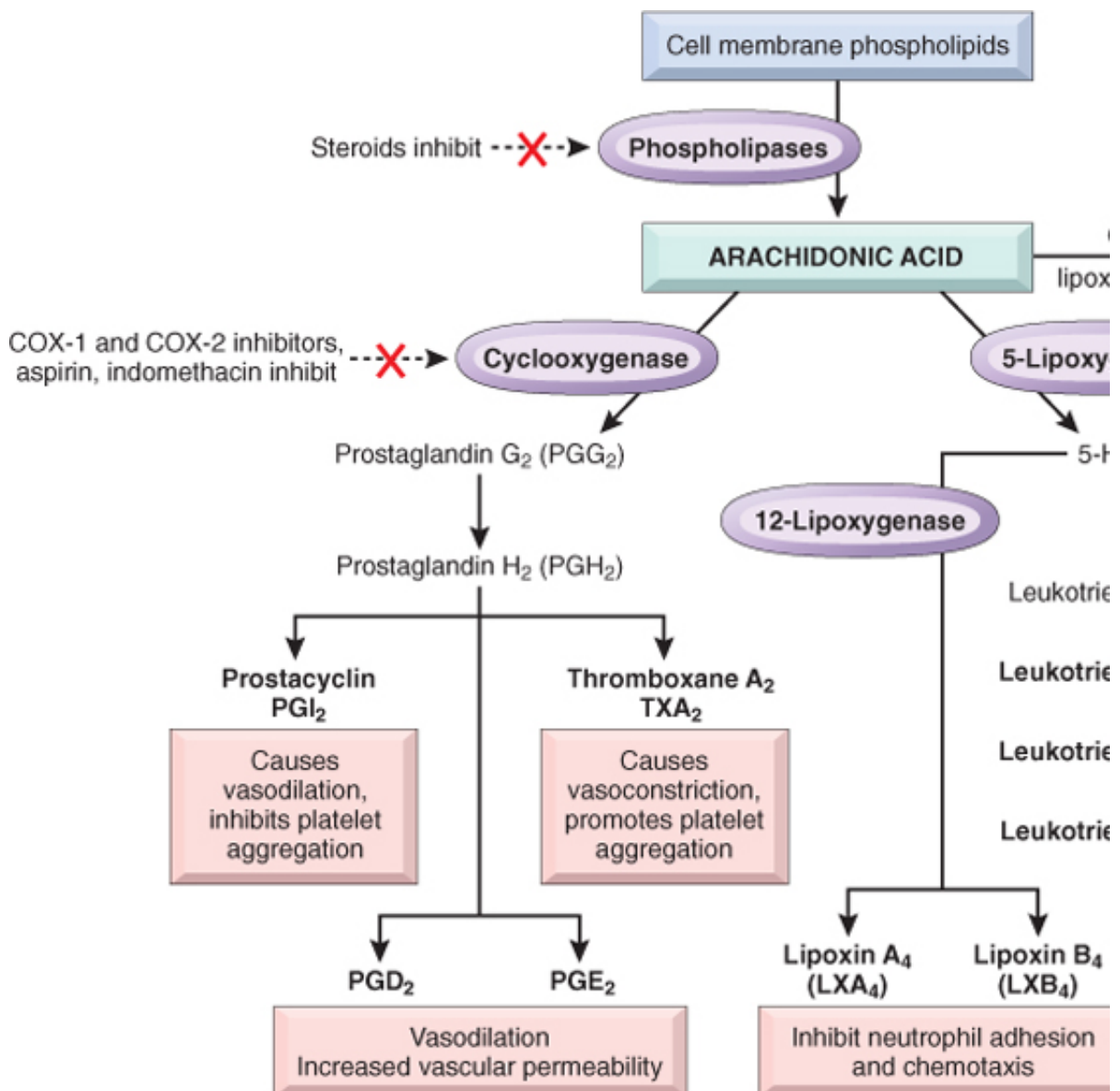


Figure 2-15 Generation of arachidonic acid metabolites and their roles in inflammation. Note the enzymatic acti intervention blocks major pathways (denoted with a red X). COX-1, COX-2, Cyclooxygenase 1 and 2; HET hydroperoxyeicosatetraenoic acid.

Originally named for its ability to aggregate platelets and cause degranulation, platelet-activating factor (PAF) is a membrane phospholipid with a broad spectrum of inflammatory effects. PAF is *acetyl glycerol ether phospholipid* derived from membrane phospholipids of neutrophils, monocytes, basophils, endothelial cells, and platelets (ar phospholipase A<sub>2</sub>). PAF acts directly on target cells via a specific G-protein-coupled receptor. In a causes vasoconstriction and bronchoconstriction and is 100 to 1,000 times more potent than is histamine. PAF causes increased vascular permeability. PAF can elicit most of the reactions of inflammation, including leukocyte degranulation, and the oxidative burst; it also stimulates the synthesis of other mediator

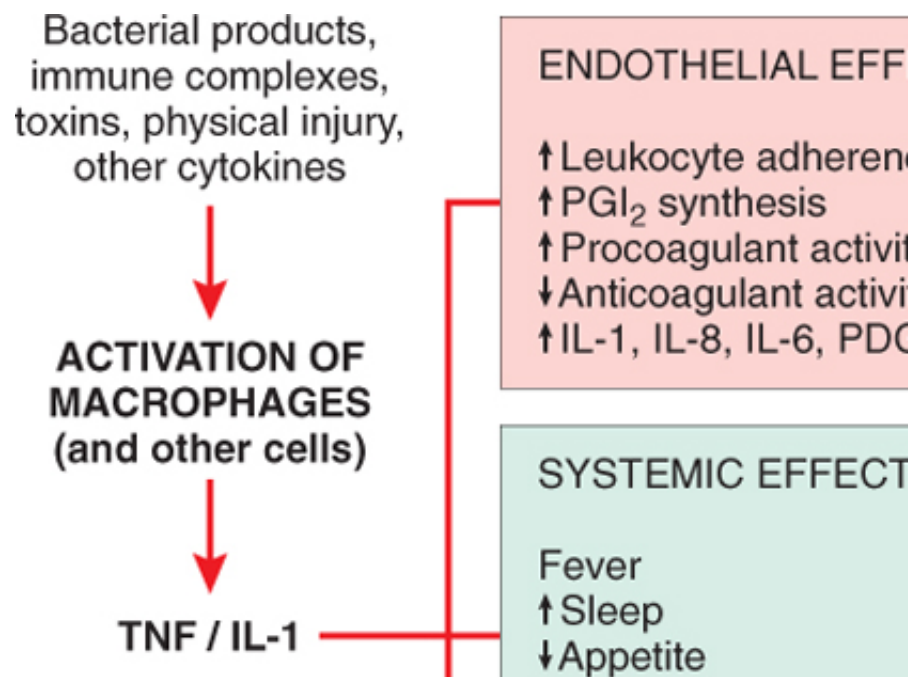
### Cytokines

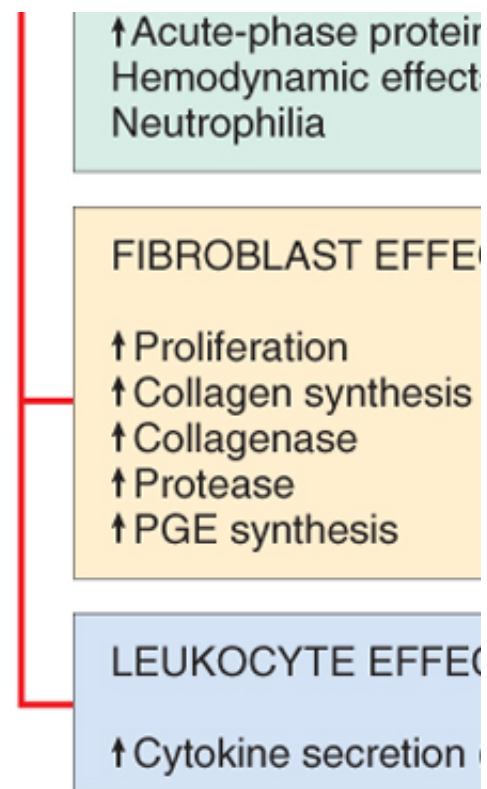
Cytokines are polypeptide products of many cell types that function as mediators of inflammation. Different cytokines are involved in the earliest immune and inflammatory reactions to noxious stimuli. Some cytokines stimulate immune responses to microbes. Some cytokines stimulate bone marrow precursors to produce more that are consumed during inflammation and immune responses. Molecularly characterized cytokines (and numbered), referring to their ability to mediate communications between leukocytes. However, many cytokines that do act on leukocytes are not called interleukins, for hist

The major cytokines in acute inflammation are TNF and IL-1, as well as a group of chemoattractant cytokines that are more important in chronic inflammation include interferon-γ (IFN-γ) and IL-12.

### Tumor Necrosis Factor and Interleukin-1

TNF and IL-1 are produced by activated macrophages, as well as mast cells, endothelial cells, and during adaptive immune responses. The principal role of these cytokines in inflammation is in *endothelial* stimulate the expression of adhesion molecules on endothelial cells, resulting in increased leukocyte adhesion. TNF also stimulates the production of additional cytokines (notably chemokines) and eicosanoids. TNF also increases causes aggregation and activation of neutrophils, and IL-1 activates tissue fibroblasts, resulting in ECM.





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Figure 2-16 Major effects of tumor necrosis factor (TNF) and interleukin 1 (IL-1) in inflammation. PDGF, Platelet-derived growth factor; PGE, prostaglandin E.

Although TNF and IL-1 are secreted by macrophages and other cells at sites of inflammation, they can also act at distant sites to induce the *systemic acute-phase reaction* that is often associated with infection and trauma. Manifestations of this reaction include fever, lethargy, hepatic synthesis of various acute-phase proteins, metabolic changes, and release of adrenocorticotrophic hormone (inducing corticosteroid synthesis). Other manifestations of inflammation are described later in the chapter.

### Chemokines

The *chemokines* are a family of small (8-10 kD), structurally related proteins that act primarily as chemoattractants for leukocytes. The two main functions of chemokines are in leukocyte recruitment in inflammation and in the development of cells in lymphoid and other tissues. Combinations of chemokines that are produced transiently in particular cell populations (e.g., neutrophils, eosinophils, or lymphocytes) to sites of inflammation. One consequence of such activation, which was mentioned earlier, is increased affinity of leukocyte cells. Some chemokines are produced constitutively in tissues and are responsible for the anatomical organization of cell populations in tissues (e.g., the segregation of T and B lymphocytes in different areas of lymph nodes). Chemokines are displayed bound to proteoglycans on endothelial cells or in the ECM, providing high local concentration. Chemokines mediate their activities by binding to specific G-protein-coupled receptors on target cells. CXCR4 and CCR5 are important coreceptors for the binding and entry of the human immunodeficiency virus (Chapter 5).

Chemokines are classified into four groups based on the arrangement of highly conserved cysteine residues: CXC and CC chemokines:

CXC chemokines have one amino acid separating the conserved cysteines and act primarily as neutrophil chemoattractants; it is produced by activated macrophages, endothelial cells, mast cells, and fibroblasts. CC chemokines have adjacent cysteine residues. Examples include chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein 1α (MIP-1α) (both produced by macrophages). RANTES (regulated on activation normal T expressed and secreted) (chemotactic for monocytes).

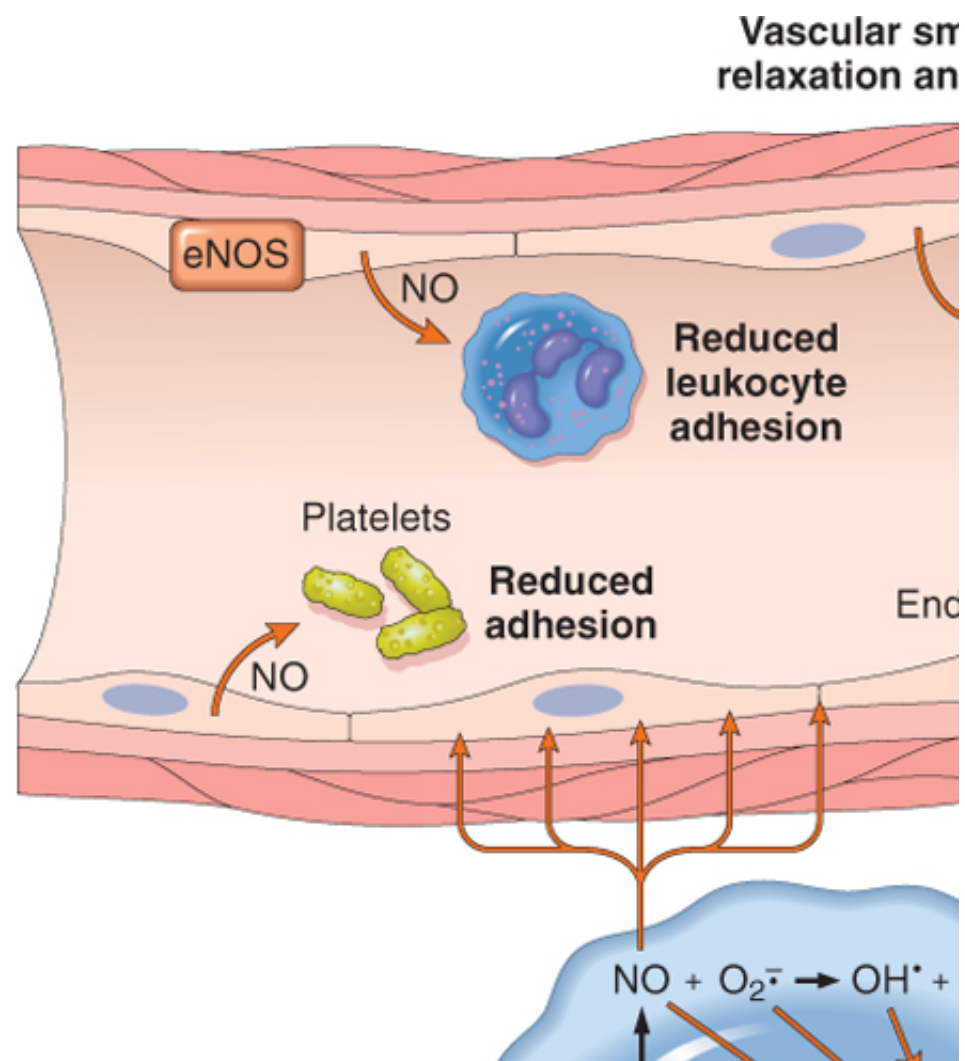
monocytes), MCP-1 (regulated on activation normal T-expressed and secreted) (chemotactic for monocytes), and eotaxin (chemotactic for eosinophils).

### Reactive Oxygen Species

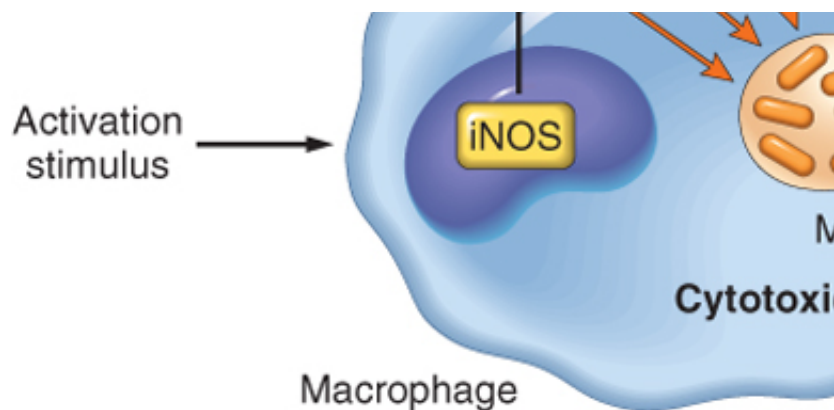
ROS are synthesized via the NADPH oxidase (phagocyte oxidase) pathway and are released from activated by microbes, immune complexes, cytokines, and a variety of other inflammatory stimuli. oxygen-derived free radicals were described in [Chapter 1](#), in the context of cell injury. When the F function to destroy phagocytosed microbes and necrotic cells, much like NO. When secreted at lo cytokine, and adhesion molecule expression, thus amplifying the cascade of inflammatory mediators responsible for tissue injury by several mechanisms, including (1) endothelial damage, with throm protease activation and antiprotease inactivation, with a net increase in breakdown of the ECM; a (e.g., tumor cells, erythrocytes, parenchymal cells). Fortunately, various antioxidant protective me dismutase, and glutathione) are present in tissues and blood to minimize the toxicity of the oxygen

### Nitric Oxide

NO is a short-lived, soluble, free-radical gas produced by many cell types and capable of mediating central nervous system it regulates neurotransmitter release as well as blood flow. Macrophages microbes and tumor cells. When produced by endothelial cells (where it was originally named *endothelium-derived relaxing factor*) causes smooth muscle relaxation and vasodilation.







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Figure 2-17 Sources and effects of nitric oxide<sub>P<sub>x</sub></sub> (NO) in inflammation. NO synthesized by endothelial cells (mac [eNOS]) and by macrophages (mostly via inducible [type II] NO synthase [iNOS]) causes vasodilation and reduces phagocytes is also cytotoxic to microbes.

NO is synthesized de novo from L-arginine, molecular oxygen, and NADPH by the enzyme nitric oxide synthase (NOS), with different tissue distributions. Type I (nNOS) is a constitutively expressed enzyme with a significant role in inflammation. Type II (iNOS) is an inducible enzyme present in macrophages and a number of inflammatory cytokines and mediators, most notably by IL-1, TNF, and IFN- $\gamma$ , and by the production of NO in inflammatory reactions. iNOS is also present in many other cell types, including respiratory epithelium. Type III (eNOS) is a constitutively synthesized NOS found primarily (but not

NO plays many roles in inflammation (see Fig. 2-17), including (1) relaxation of vascular smooth muscle, (2) inhibition of all stages of platelet activation (adhesion, aggregation, and degranulation), (3) reduction of leukocyte adhesion, and (4) action as a microbicidal (cytotoxic) agent (with or without superoxide radicals) in activated macrophages.

### Lysosomal Enzymes of Leukocytes

The lysosomal granules of neutrophils and monocytes contain many molecules that can mediate tissue damage. These are released after cell death, by leakage during the formation of the phagocytic vacuole, or during futile attempts to digest indigestible surfaces, as described earlier. The most important of these lysosomal molecules are cathepsins, which are optima and are generally active only within phagolysosomes, whereas *neutral proteases*, including trypsin, chymotrypsin, and elastase, are active in the ECM and cause destructive, deforming tissue injury by degrading elastin, collagen, and other proteins. Neutral proteases can also cleave the complement proteins C3 and C5 directly to generate C3a and C5a and can generate bradykinin-like peptides from kininogen.

The potentially damaging effects of lysosomal enzymes are checked by *antiproteases* present in the blood, including  $\alpha_1$ -antitrypsin, the major inhibitor of neutrophil elastase, and  $\alpha_2$ -macroglobulin. Deficiencies of the activation of leukocyte proteases, resulting in tissue destruction at sites of leukocyte accumulation, as in the lung can cause a severe panacinar emphysema (Chapter 13).

### Neuropeptides

Like the vasoactive amines, neuropeptides can initiate inflammatory responses; these are small peptides that transmit pain signals, regulate vessel tone, and modulate vascular permeability. Nerve fibers that are prominent in the lung and gastrointestinal tract.

## SUMMARY

**Major Cell-derived Mediators of Inflammation**  
**Vasoactive amines:** histamine, serotonin, and substance P. Effects are vasodilation and increased vascular permeability.  
**Arachidonic acid metabolism:** prostaglandins and leukotrienes; several forms exist and are involved in vasodilation, chemotaxis, and other reactions of inflammation; antagonized by lipoxins.  
**Cytokines:** by many cell types; usually act at short range; mediate multiple effects, mainly recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and IL-6.  
**Chemokines:** recruit leukocytes; principal ones in acute inflammation are CXCL8 (IL-8) and CXCL12 (SDF-1).  
**Reactive oxygen species:** role in microbial killing, tissue injury, and signaling.

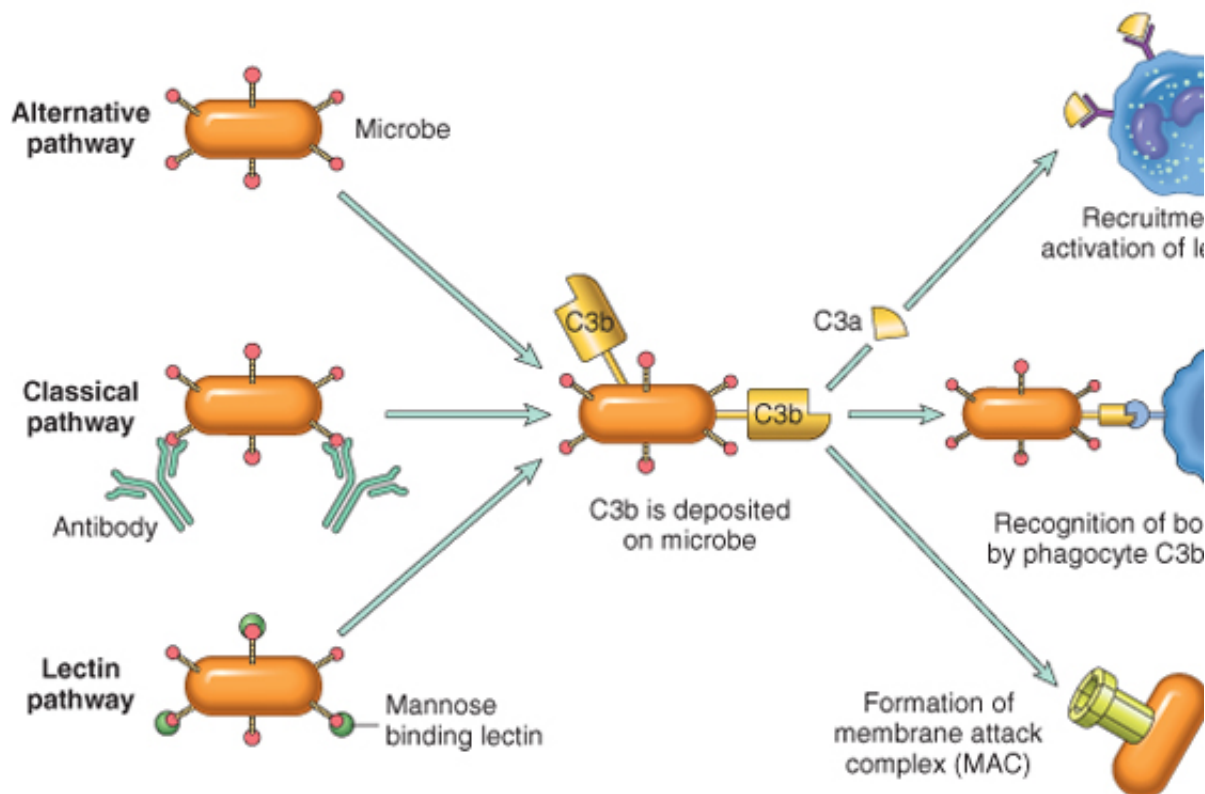
chemokines *Reactive oxygen species*: role in microbial killing, tissue injury  
 microbial killing *Lysosomal enzymes*: role in microbial killing, tissue injury

## Plasma Protein-Derived Mediators

Circulating proteins of three interrelated systems—the complement, kinin, and coagulation systems—inflammatory reaction.

### Complement

The *complement system* consists of plasma proteins that play an important role in host defense (i.e., activation, different complement proteins coat (opsonize) particles, such as microbes, for phagocytosis, the inflammatory response by increasing vascular permeability and leukocyte chemotaxis. Complement forms a porelike membrane attack complex (MAC) that punches holes in the membranes of invading microbes.



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Figure 2-18 The activation and functions of the complement system. Activation of complement by different pathways of the complement system are mediated by breakdown products of C3 and other complement proteins, and by

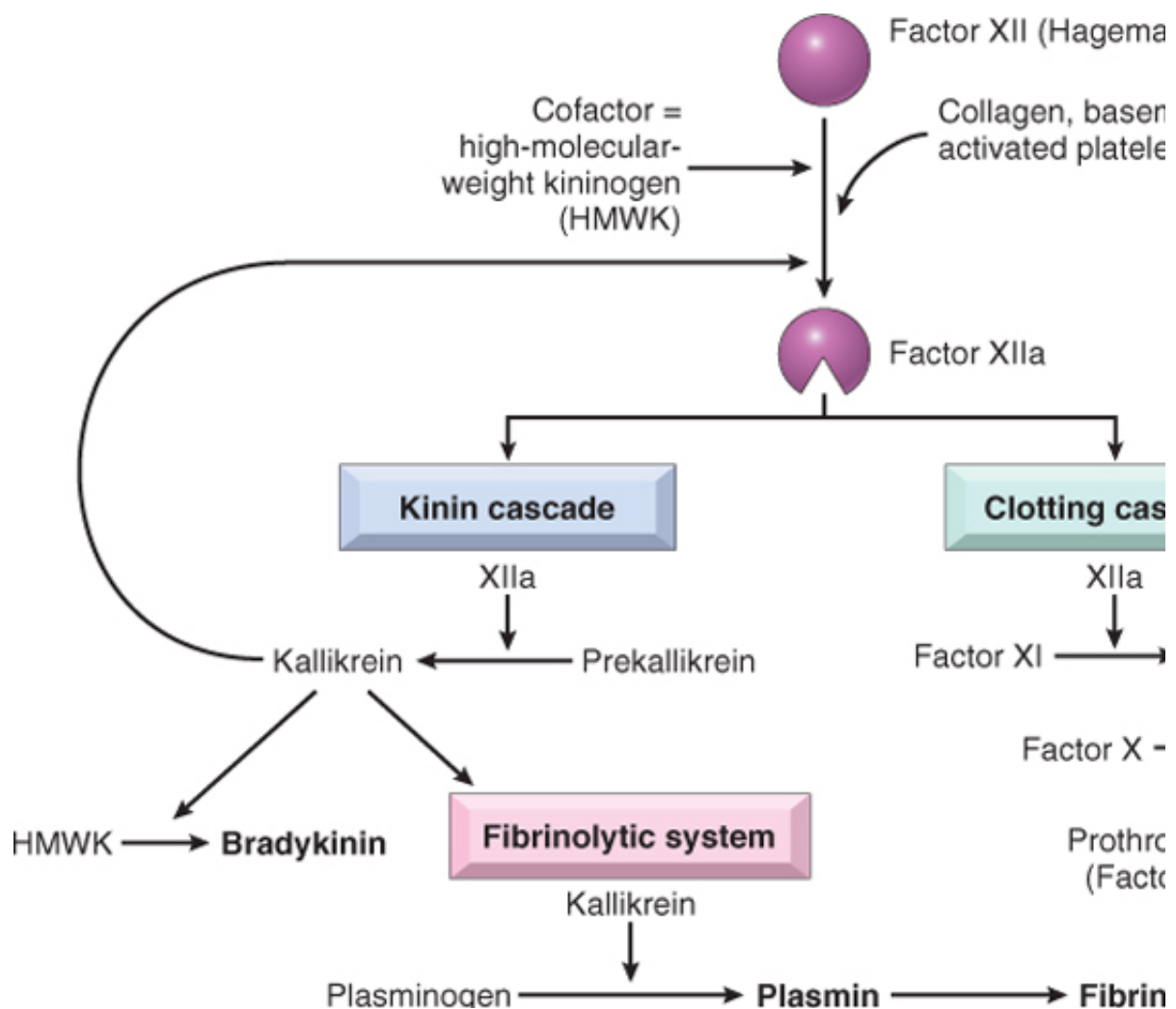
Complement components (numbered C1 to C9) are present in plasma in inactive forms, and many of them themselves acquire proteolytic activity, thus setting up an enzymatic cascade. The critical step in the activation of complement is the activation of the third component, C3 (Fig. 2-18). C3 cleavage occurs by three pathways: (1) by fixation of the first complement component C1 to antigen-antibody complexes; (2) through the *lectin pathway*, in which a plasma lectin binds to microbial polysaccharides (e.g., endotoxin) and other microbial cell-wall components, and involving a distinct *properdin* and *factors B* and *D*; and (3) by the *lectin pathway*, in which a plasma lectin binds to microbial polysaccharides (e.g., endotoxin) and other microbial cell-wall components, and involving a distinct *properdin* and *factors B* and *D*. All three pathways lead to the activation of *convertase* that cleaves C3 to C3a and C3b. C3b deposits on the cell or microbial surface where it

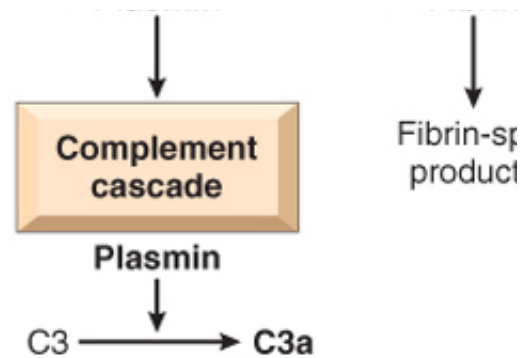
convertase that cleaves C5 to C5a and C5b. C5b depends on the C3 convertase complex to form C5 convertase; this complex cleaves C5 to generate C5a and an assembly of C6 to C9. There are many connections between the various circulating systems of inflammation. **thrombin** (generated during blood coagulation) may cleave C5, thus triggering the complement pathway. The products that are produced along the way affect a variety of phenomena in acute inflammation:

**Vascular effects.** C3a and C5a increase vascular permeability and cause vasodilation by increasing the production of histamine. These complement products are also called *anaphylatoxins* because their actions mimic the cellular effectors of the severe allergic reaction called anaphylaxis (Chapter 5). C5a also affects metabolism in neutrophils and macrophages, causing release of more inflammatory mediators. **chemotaxis.** C5a activates leukocytes, increasing their adhesion to endothelium, and is a potent attractant for monocytes, eosinophils, and basophils. **Phagocytosis.** When fixed to a microbial surface, C3b and iC3b act as opsonins, augmenting phagocytosis by neutrophils and macrophages, which engulf the microbes.

The activation of complement is tightly controlled by cell-associated and circulating *regulatory proteins*. Defects in these host cell membranes protect normal cells from inappropriate damage during protective reactions. Overactivation or excessive complement activation (e.g., in antibody-mediated diseases) can overwhelm the system, and why complement activation is responsible for serious tissue injury in a variety of immunologic disorders.

#### Coagulation and Kinin Systems





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Figure 2-19 Interrelationships among the four plasma mediator systems triggered by activation of factor X

A central event in the generation of several circulating mediators of inflammation is activation of Hageman factor (factor XIIa) initiates four systems involved in the inflammatory response: (1) the kinins; (2) the clotting system, inducing the activation of **thrombin**, fibrinopeptides, and factor X; (3) the fibrinolytic system, producing plasmin and inactivating thrombin; and (4) the complement system, producing C3a and C5a. Hageman factor (also known as *factor XII* of the *intrinsic coagulation cascade*) is a protein synthesized in an inactive form until it encounters collagen, basement membrane, or activated platelets (e.g., at the assistance of a high-molecular-weight kininogen (HMWK) cofactor, factor XII then undergoes a conformational change to factor XIIa), exposing an active serine center that can cleave several protein substrates of the kinin and clotting systems.

In the *clotting system* (Chapter 4), the factor XIIa-driven proteolytic cascade leads to activation of factor X, which cleaves soluble fibrinogen to generate an insoluble *fibrin clot*. *Factor Xa*, an intermediate in the clotting cascade, increases vascular permeability and leukocyte emigration. **Thrombin** participates in inflammation by binding to protease-activated receptors expressed on platelets, endothelial cells, and many other cell types. Binding of **thrombin** to these receptors leads to their activation and enhanced leukocyte adhesion. In addition, **thrombin** generates *fibrinopeptides*, which increase vascular permeability and are chemotactic for leukocytes.

While activated Hageman factor is inducing clotting, it is concurrently activating the *fibrinolytic system* by cleaving fibrin, thereby solubilizing the fibrin clot. Without fibrinolysis and other regulatory mechanisms, the coagulation cascade, even by trivial injury, would culminate in continuous and irrevocable clotting. *Plasminogen activator* (released from endothelium, leukocytes, and other tissues) and *kallikrein* can bind up in the evolving fibrin clot. The resulting product, *plasmin*, is a multifunctional protease that is important in lysing clots. However, fibrinolysis also participates in multiple steps in the vascular response. Fibrin degradation products increase vascular permeability, while plasmin cleaves the C3 complement component into C3a and vasodilation and increased vascular permeability. Plasmin can also activate Hageman factor, thus amplifying the inflammatory responses.

*Kinin system* activation leads ultimately to the formation of *bradykinin* from its circulating precursor *angiotensin I*. *Bradykinin* causes increased vascular permeability, arteriolar dilation, and bronchial smooth muscle contraction. The actions of *bradykinin* are short-lived because it is rapidly degraded by *angiotensinase*. It is important to note that *kallikrein*, an intermediate in the kinin cascade with chemotactic activity, is a protease and is thus another link between the kinin and clotting systems.

## SUMMARY

**Plasma Protein-Derived Mediators of Inflammation**  
**Complement proteins:** Activation of the complement system by microbes or antibodies leads to the generation of membrane attack complex (MAC) and other products, which are responsible for leukocyte chemotaxis, opsonization and killing of pathogens, and cell killing.  
**Coagulation proteins:** Activated factor XII (factor XIIa) and complement cascades, and activates the fibrinolytic system.  
**Kinins:** Produced by cleavage of precursors; mediate vascular reaction, pain



It is evident from the preceding discussion that many molecules are involved in different aspects of inflammation. These molecules often interact with, amplify, and antagonize one another. From this almost bewildering array of mediators, it is not possible to identify the major contributors to various components of acute inflammation (Table 2-6). Despite our increasing understanding of these mediators, we still do not fully understand why some stimuli elicit inflammation. As mentioned from the outset that necrotic cells are a powerful stimulus for inflammation, but how this is established. Hypoxia itself induces an inflammatory response, in part by stimulating the production of reactive oxygen species that increase vascular permeability.

**Table 2-6. Role of Mediators in Different Reactions of Inflammation**

<b>Vasodilation</b>	Prostaglandins
	Nitric oxide <sub>Rx</sub>
	Histamine
<b>Increased vascular permeability</b>	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells) Bradykinin Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub> PAF Substance P
<b>Leukocyte recruitment and activation</b>	TNF, IL-1 Chemokines C3a, C5a Leukotriene B <sub>4</sub> (Bacterial products, e.g., <i>N</i> -formyl methyl peptides)
<b>Fever</b>	IL-1, TNF
	Prostaglandins
<b>Pain</b>	Prostaglandins
	Bradykinin
	Neuropeptides
<b>Tissue damage</b>	Lysosomal enzymes of leukocytes
	Reactive oxygen species
	Nitric oxide <sub>Rx</sub>

IL-1, Interleukin-1; PAF, platelet-activating factor; TNF, tumor necrosis factor.



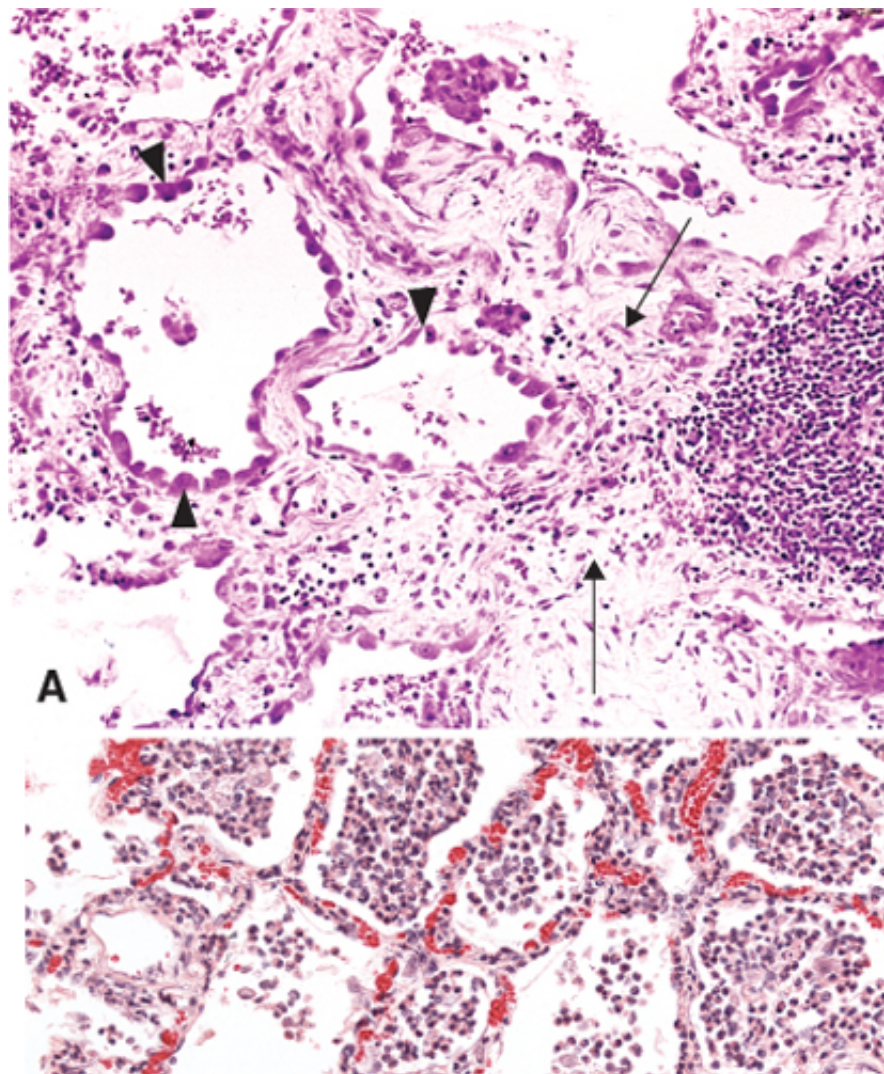


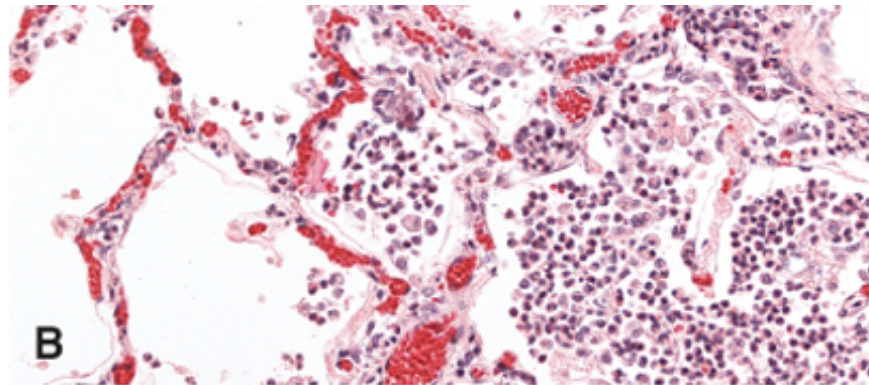
## CHRONIC INFLAMMATION

*Chronic inflammation* is inflammation of prolonged duration (weeks to months to years) in which a *healing proceed simultaneously*. In contrast to acute inflammation, which is distinguished by vascular changes and a predominantly neutrophilic infiltrate, chronic inflammation is characterized by (Fig. 2-20; also see |

*Infiltration with mononuclear cells*, including macrophages, lymphocytes, and plasma cells;  
*Repair, involving new vessel proliferation (angiogenesis)*

As indicated in [Figure 2-8](#), acute inflammation may progress to chronic inflammation. This transition cannot be resolved, either because of the persistence of the injurious agent or because of interference with healing. For example, a peptic ulcer of the duodenum initially shows acute inflammation followed by the healing process. However, recurrent bouts of duodenal epithelial injury interrupt this process and result in a lesion characterized by chronic inflammation ([Chapter 15](#)). Alternatively, some forms of injury (e.g., viral infections) engender a persistent inflammation from the onset.





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Figure 2-20 **A**, Chronic inflammation in the lung, showing the characteristic histologic features: collection of chro  
parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, *arrowheads*), and replacemen  
contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spac

Chronic inflammation arises in the following settings:

*Persistent infections* by microbes that are difficult to eradicate. These include mycobacteria (organism of syphilis), and certain viruses and fungi, all of which tend to establish persistent mediated immune response called *delayed-type hypersensitivity* (Chapter 5). In fact, most reactions dominated by lymphocytes and macrophages. *Immune-mediated inflammatory diseases* that are caused by excessive and inappropriate activation of the immune system important health problems (Chapter 5). Under certain conditions, immune reactions develop leading to *autoimmune diseases*. In these diseases, autoantigens evoke a self-perpetuating tissue damage and inflammation. Inflammation secondary to autoimmunity plays an important role in debilitating chronic diseases, such as rheumatoid arthritis and inflammatory bowel disease. *Environmental substances* are the cause of *allergic diseases*, such as bronchial asthma. In morphologic patterns of mixed acute and chronic inflammation because they are characteristic. Because the eliciting antigens cannot be eliminated, these disorders tend to be chronic and *potentially toxic agents*. Examples include nondegradable exogenous materials such as inhaled dust in a chronic inflammatory response in the lungs (*silicosis*, Chapter 13), and endogenous age-related lipid components, which may contribute to *atherosclerosis* (Chapter 10).

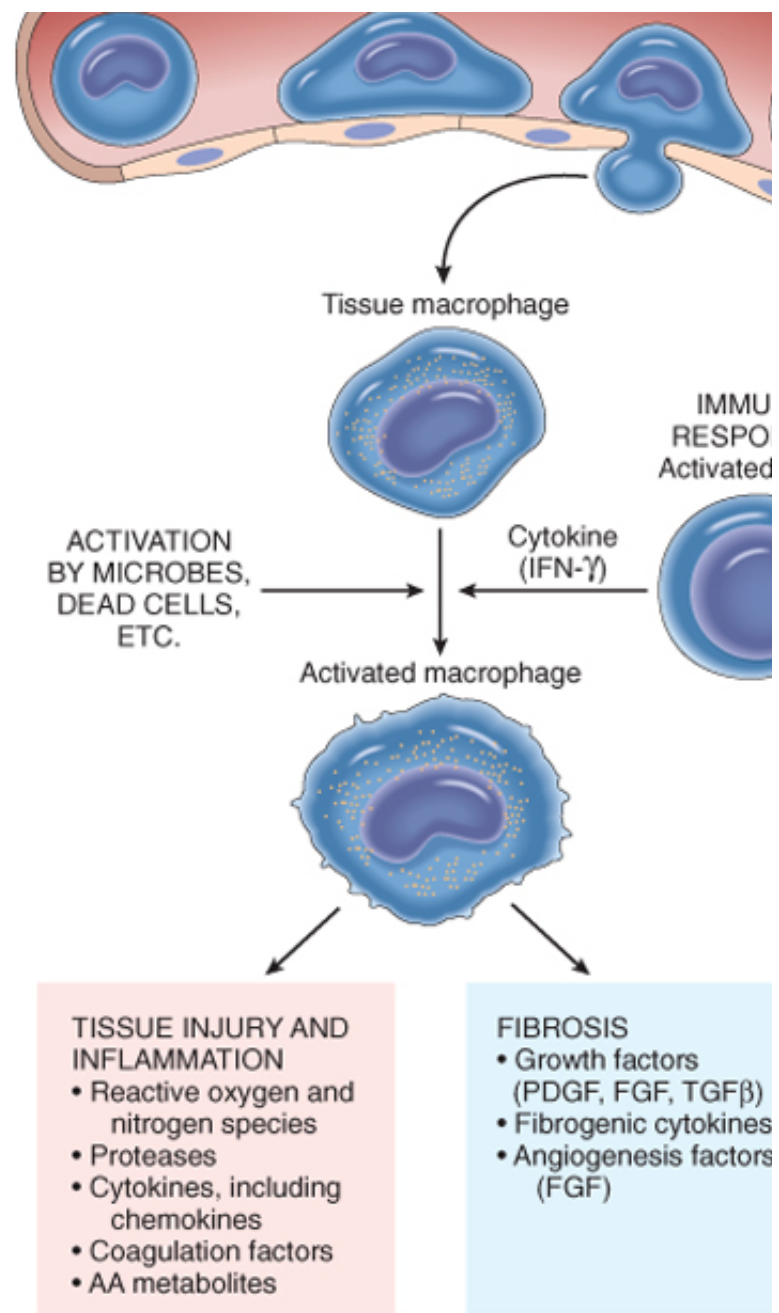
### Chronic Inflammatory Cells and Mediators

A fundamental feature of chronic inflammation is its persistence, and this results from complex interactions of recruited cells to the site of inflammation and are activated at this site. Understanding the pathogenesis of chronic inflammation requires an appreciation of these cells and their biologic responses and functions.

#### Macrophages

*Macrophages*, the dominant cells of chronic inflammation, are tissue cells derived from circulating monocytes from the bloodstream. Macrophages are normally diffusely scattered in most connective tissues, such as the liver (where they are called *Kupffer cells*), spleen and lymph nodes (called *sinus histiocytes*), and in the lungs (*alveolar macrophages*). Together these cells comprise the so-called *mononuclear phagocyte system* of reticulo-endothelial system. In all tissues, macrophages act as filters for particulate matter, microorganisms, acting as sentinels to alert the specific components of the adaptive immune system (T and B lymphocytes).





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Figure 2-21 The roles of activated macrophages in chronic inflammation. Macrophages are activated by nonimmune antigens, including microbes, dead cells, and cytokines from immune-activated T cells, particularly interferon- $\gamma$  (IFN- $\gamma$ ). The products made by activated macrophages are indicated. AA, Arachidonic acid; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; T

The half-life of circulating monocytes is about 1 day; under the influence of adhesion molecules they migrate to a site of injury within 24 to 48 hours after the onset of acute inflammation, as described in extravascular tissue, they undergo transformation into larger macrophages, which have longer half-lives and more phagocytosis than do blood monocytes. Macrophages may also become *activated*, resulting in increased lysosomal enzymes, more active metabolism, and greater ability to kill ingested organisms. By light microscopy they appear large, flat, and pink (in H&E stains); this appearance may be similar to that of squamous epithelial cells and are therefore sometimes called *epithelioid cells*. Activation signals include bacterial products and cytokines secreted by sensitized T lymphocytes (in particular the cytokine IFN- $\gamma$ ), various mediators of inflammation, and ECM proteins such as fibronectin. After activation, macrophages secrete a wide variety of bio



unchecked, can result in the tissue injury and fibrosis that are characteristic of chronic inflammatory

*Acid and neutral proteases.* Recall that the latter were also implicated as mediators of tissue enzymes, such as *plasminogen activator*, greatly amplify the generation of proinflammatory *metabolites (eicosanoids)*. Cytokines such as IL-1 and TNF, as well as a variety of *growth factors*, stimulate smooth muscle cells and fibroblasts and the production of ECM

After the initiating stimulus is eliminated and the inflammatory reaction abates, macrophages eventually return to normal. In chronic inflammatory sites, however, macrophage accumulation persists, and macrophage activation by lymphocyte-derived chemokines and other cytokines is an important mechanism by which macrophages perpetuate inflammatory sites. IFN- $\gamma$  can also induce macrophages to fuse into large, multinucleated cells called

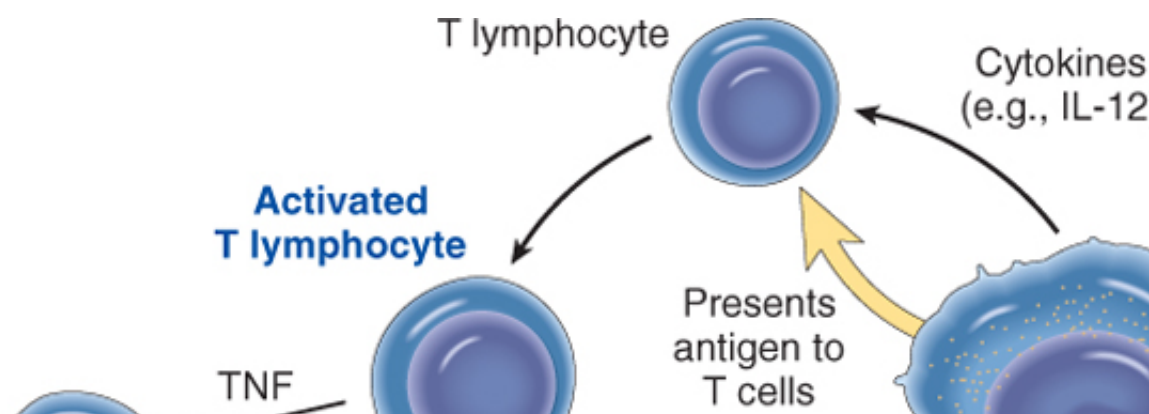
#### *Lymphocytes, Plasma Cells, Eosinophils, and Mast Cells*

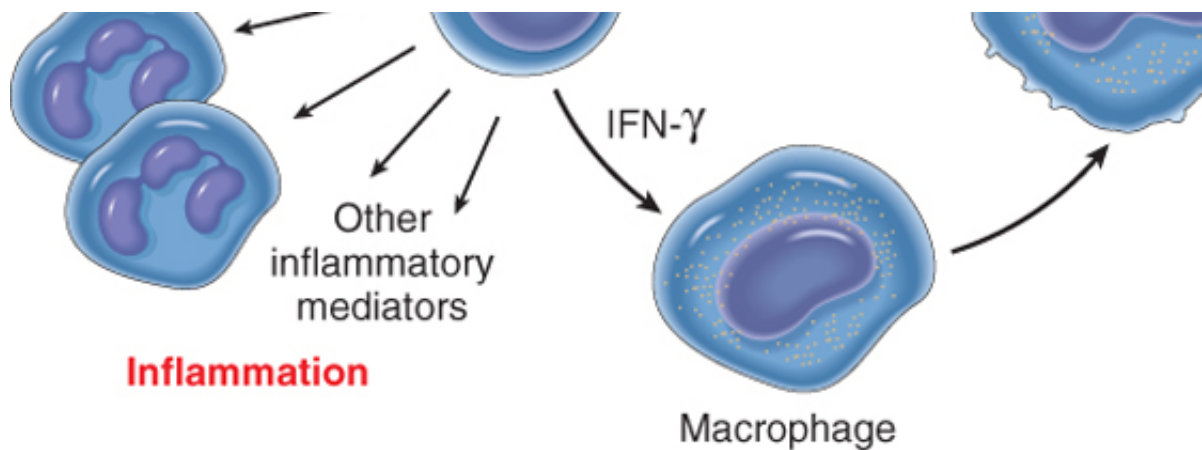
Lymphocytes are mobilized to the setting of any specific immune stimulus (i.e., infections) as well as (e.g., due to infarction or tissue trauma). Both T and B lymphocytes migrate into inflammatory sites and release cytokine pairs and chemokines that recruit other leukocytes. Lymphocytes and macrophages interact; these interactions play an important role in chronic inflammation (Fig. 2-22). Macrophages display antigen molecules (called *costimulators*), and produce cytokines (notably IL-12) that stimulate T-cell responses. T lymphocytes, in turn, produce cytokines, and one of these, IFN- $\gamma$ , is a powerful activator of macrophage antigen presentation and cytokine secretion. The result is a cycle of cellular reactions that fuel and sustain chronic inflammation. B lymphocytes develop from activated B lymphocytes and produce antibodies directed either against persistent antigens or altered tissue components. In some strong chronic inflammatory reactions, the accumulation of lymphocytes and plasma cells may assume the morphologic features of lymphoid organs, and akin to lymph nodes, lymphoid centers. This pattern of lymphoid organogenesis is often seen in the synovium of patients with long-standing

*Eosinophils* are characteristically found in inflammatory sites around parasitic infections or as part of allergic reactions typically associated with *allergies*. Their recruitment is driven by adhesion molecules similar to those that recruit neutrophils (e.g., eotaxin) derived from leukocytes or epithelial cells. Eosinophil granules contain cationic proteins that are toxic to parasites but also causes epithelial cell necrosis.

*Mast cells* are sentinel cells widely distributed in connective tissues throughout the body, and they play a key role in inflammatory responses. In atopic individuals (individuals prone to allergic reactions), mast cells are activated by certain environmental antigens. When these antigens are subsequently encountered, the IgE-coated mast cells release histamines and AA metabolites that elicit the early vascular changes of acute inflammation. IgE-antigen complexes also play a role in *allergic reactions*, including *anaphylactic shock* (Chapter 5). Mast cells can also elaborate cytokines, which may play a beneficial role in some infections.

An important final point: *although neutrophils are the classic hallmarks of acute inflammation, macrophages nevertheless continue to show extensive neutrophilic infiltrates*, as a result of either persistent microorganisms or antigens elaborated by macrophages.





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 Figure 2-22 Macrophage-lymphocyte interactions in chronic inflammation. Activated lymphocytes and macrophages release inflammatory mediators that affect other cells. IFN- $\gamma$ , interferon- $\gamma$ ; IL-1, interleukin 1;

## Granulomatous Inflammation

Table 2-7. Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Noncaseating tubercle (granuloma prototype): fibroblasts, lymphocytes, histiocytes, occasional plasma cells; Caseating tubercle: central amorphous granular material, often with fast bacilli
Leprosy	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granuloma
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, cell infiltrate; central cells are necrotic without identifiable organisms
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central necrosis; neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacterial, self-antigens	Occasional noncaseating granulomas in wall of intestine with associated inflammatory infiltrate

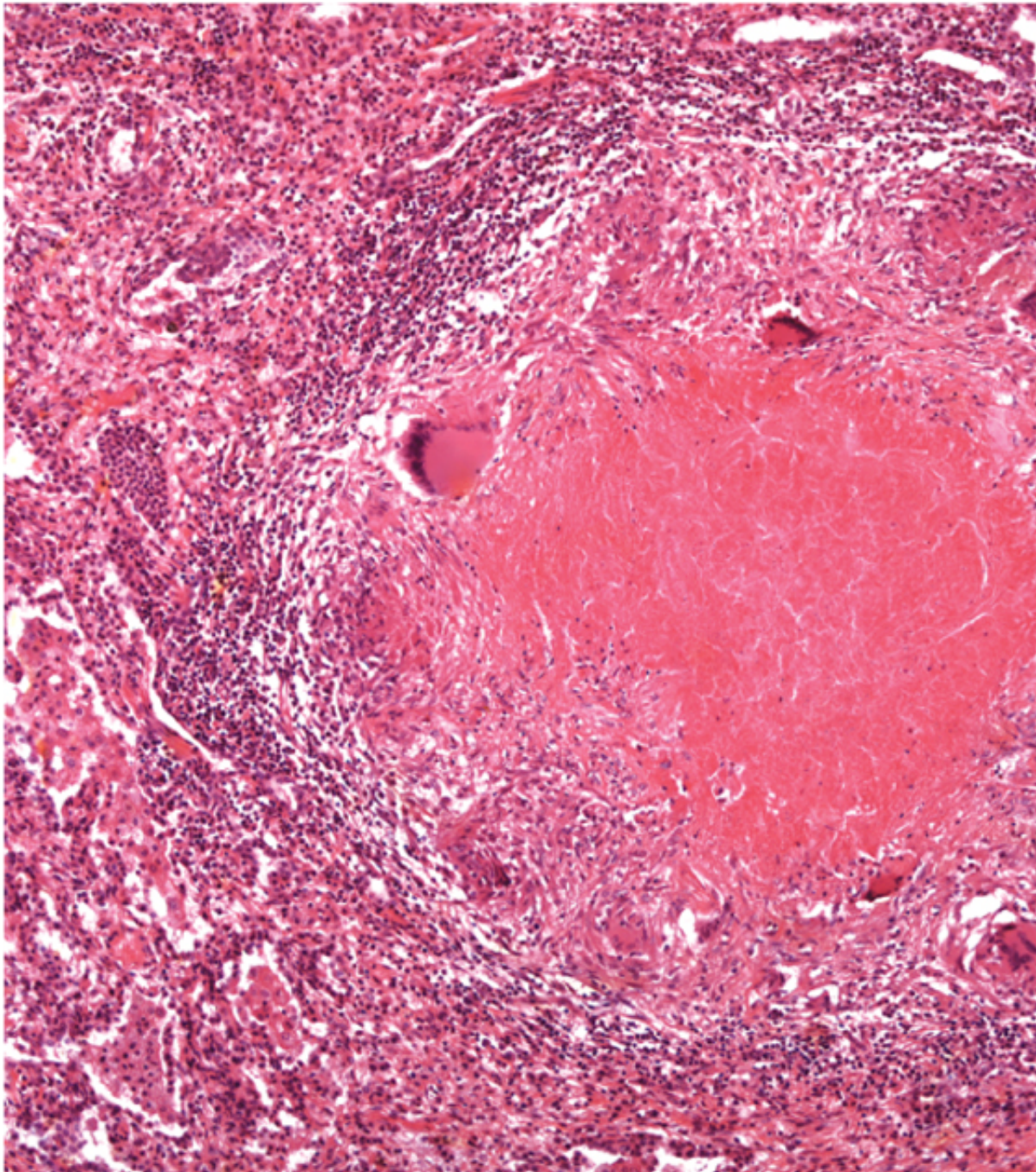
**Granulomatous inflammation** is a distinctive pattern of chronic inflammation characterized by aggregates of mononuclear cells that often assume an epithelioid appearance. Granulomas are encountered in certain specific pathologic states. The recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) in which it occurs. Granulomas can form in the setting of persistent T-cell responses to certain microbes (such as *M. tuberculosis* and *M. leprae*), where T-cell-derived cytokines are responsible for chronic macrophage activation. *Tuberculosis* is a disease caused by infection and should always be excluded as the cause when granulomas are identified. Granulomas can also form in response to relatively inert foreign bodies (e.g., suture or splinter), forming so-called *foreign body granulomas*. These granulomas effectively "wall off" the offending agent and is therefore a useful defense mechanism. In infectious diseases, granulomas always lead to eradication of the causal agent, which is frequently resistant to killing or degradation. In noninfectious diseases, subsequent fibrosis may even be the major cause of organ dysfunction in some diseases, such as in sarcoidosis.

### Morphology

In the usual H&E preparations (Fig. 2-23), epithelioid cells in granulomas have pink-staining cytoplasm and indistinct cell boundaries. The aggregates of epithelioid macrophages are surrounded by a rim of lymphocytes secreting the cytokines responsible for continuing macrophage activation. The entire aggregate may have a rim of fibroblasts and connective tissue. Frequently, but not invariably, granulomas 40 to 50  $\mu$ m in diameter are found in granulomas. They consist of a large mass of cells with foamy nuclei, and they derive from the fusion of 20 or more macrophages. In granulomas caused by infectious organisms (most classically the tubercle bacillus), a combination of hypoxia and the presence of the organism leads to a central zone of necrosis. Grossly, this has a granular, cheesy appearance.



leads to a central zone of necrosis. Grossly, this has a granular, cheesy appearance, termed **caseous necrosis** (Chapters 1 and 13). Microscopically, this necrotic material appears structureless, granular debris, with complete loss of cellular details. Healing of granuloma by fibrosis that may be quite extensive.



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Figure 2-23 A typical granuloma resulting from infection with *Mycobacterium tuberculosis* showing central caseous necrosis, many giant cells, and a peripheral accumulation of lymphocytes.

## SUMMARY

**Features of Chronic Inflammation** Prolonged host response to persistent s

microbes that resist elimination, immune responses against self and environmental  
some toxic substances (e.g. silica); underlies many medically important diseases  
coexisting inflammation, tissue injury, attempted repair by scarring, and immune  
infiltrate consists of macrophages, lymphocytes, plasma cells; fibrosis is often  
cytokines produced by macrophages and lymphocytes (notably T lymphocytes)  
interactions between these cells tend to amplify and prolong the inflammatory



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## SYSTEMIC EFFECTS OF INFLAMMATION

Anyone who has suffered through a severe bout of a viral illness (such as influenza) has experienced the systemic effects of inflammation, collectively called the *acute-phase reaction*, or the systemic inflammatory response syndrome. The cytokines *TNF*, *IL-1*, and *IL-6* are the most important mediators of the acute-phase reaction. These cytokines are produced by leukocytes (and other cell types) in response to infection or in immune reactions and are released systemically. Often *TNF* induces the production of *IL-1*, which in turn stimulates the production of *IL-6*, forming a cascade of cytokines. *TNF* and *IL-1* have similar biologic actions, although these may differ in subtle ways (see [Fig. 2-16](#)). *IL-6* stimulates the hepatic synthesis of a number of plasma proteins, described below.

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page 58

The acute-phase response consists of several clinical and pathologic changes.

*Fever*, characterized by an elevation of body temperature, usually by 1° to 4°C, is one of the most prominent manifestations of the acute-phase response, especially when inflammation is caused by infection. Fever is produced in response to substances called *pyrogens* that act by stimulating prostaglandin (PG) synthesis in the vascular and perivascular cells of the hypothalamus. Bacterial products, such as lipopolysaccharide (LPS; called *exogenous pyrogens*), stimulate leukocytes to release cytokines such as *IL-1* and *TNF* (called *endogenous pyrogens*) that increase the levels of cyclooxygenases that convert AA into prostaglandins. In the hypothalamus the PGs, especially *PGE<sub>2</sub>*, stimulate the production of neurotransmitters, which function to reset the temperature set point at a higher level. NSAIDs, including *aspirin*<sup>®</sup>, reduce fever by inhibiting cyclooxygenase and thus blocking PG synthesis. An elevated body temperature has been shown to help amphibians ward off microbial infections, and it is assumed that fever does the same for mammals, although the mechanism is unknown. *Elevated plasma levels of acute-phase proteins*, which are plasma proteins, mostly synthesized in the liver, whose concentrations may increase several 100-fold as part of the response to inflammatory stimuli. Three of the best-known of these proteins are C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein. Synthesis of these molecules by hepatocytes is up-regulated by cytokines, especially *IL-6*. Many acute-phase proteins, such as CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement, thus promoting the elimination of the microbes. Fibrinogen binds to erythrocytes and causes them to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes. This is the basis for measuring the *erythrocyte sedimentation rate (ESR)* as a simple test for the systemic inflammatory response, caused by any number of stimuli, including LPS. Elevated serum levels of CRP are now used as a marker for increased risk of myocardial infarction or stroke in patients with atherosclerotic vascular disease. It is believed that inflammation is involved in the development of atherosclerosis ([Chapter 10](#)), and increased CRP is a measure of inflammation. *Leukocytosis* is a common feature of inflammatory reactions, especially those induced by bacterial infection. The leukocyte count usually climbs to 15,000 or 20,000 cells/ $\mu$ L, but sometimes it may reach extraordinarily high levels, as high as 40,000 to 100,000 cells/ $\mu$ L. These extreme elevations are referred to as *leukemoid reactions* because they are similar to the white cell counts obtained in leukemia. The leukocytosis occurs initially because of accelerated release of cells from the bone marrow postmitotic reserve pool (caused by cytokines, including *TNF* and *IL-1*) and is therefore associated with a rise in the number of more immature neutrophils in the blood (*shift to the left*). Prolonged infection also stimulates production of colony-stimulating factors (CSFs), leading to

infection also stimulates production of colony-stimulating factors (CSFs), leading to increased bone marrow output of leukocytes, which compensates for the loss of these cells in the inflammatory reaction. Most bacterial infections induce an increase in the blood neutrophil count, called *neutrophilia*. Viral infections, such as infectious mononucleosis, mumps, and German measles, are associated with increased numbers of lymphocytes (*lymphocytosis*). Bronchial asthma, hay fever, and parasite infestations all involve an increase in the absolute number of eosinophils, creating an *eosinophilia*. Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are paradoxically associated with a decreased number of circulating white cells (*leukopenia*), likely because of cytokine-induced sequestration of lymphocytes in lymph nodes. Other manifestations of the acute-phase response include increased heart rate and blood pressure; decreased sweating, mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin; and rigors (shivering), chills (perception of being cold as the hypothalamus resets the body temperature), anorexia, somnolence, and malaise, probably because of the actions of cytokines on brain cells. Chronic inflammation is associated with a wasting syndrome called *cachexia*, which is mainly the result of TNF-mediated appetite suppression and mobilization of fat stores. In severe bacterial infections (*sepsis*), the large amounts of organisms and LPS in the blood or extravascular tissue stimulate the production of enormous quantities of several cytokines, notably TNF, as well as IL-12 and IL-1. As a result, circulating levels of these cytokines increase, and the nature of the host response changes. High levels of TNF cause disseminated intravascular coagulation (DIC), hypoglycemia, and hypotensive shock. This clinical triad is described as *septic shock*; it is discussed in more detail in [Chapter 4](#).

## SUMMARY

**Systemic Effects of Inflammation**  
**Fever:** cytokines (TNF, IL-1) stimulate production of prostaglandins in hypothalamus  
**Production of acute-phase proteins:** C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells  
**Leukocytosis:** cytokines (colony-stimulating factors) stimulate production of leukocytes from precursors in the bone marrow  
 In some severe infections, *septic shock*: fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities; induced by high levels of TNF

Having concluded our discussion of the cellular and molecular events in acute and chronic inflammation, we must consider the changes induced by the body's attempts to heal the damage, the process of *repair*. As described next, in [Chapter 3](#), the repair begins almost as soon as the inflammatory changes have started and involves several processes, including cell proliferation and differentiation, and ECM deposition.

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### 3 Tissue Repair: Regeneration, Healing, and Fibrosis

Critical to the survival of an organism is the ability to repair the damage caused by toxic insults and inflammation. The inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair. *Repair* refers to the restoration of tissue architecture and function after an injury. It occurs by two types of reactions (Fig. 3-1). Some tissues are able to replace the damaged components and essentially return to a normal state; this process is called *regeneration*. If the injured tissues are incapable of complete restitution, or if the supporting structures of the tissue are severely damaged, repair occurs by laying down of connective (fibrous) tissue, a process termed *healing* that results in *scar formation*. Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function. After many common types of injury, both regeneration and scar formation contribute in varying degrees to the ultimate repair. The term *fibrosis* is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an inflammatory exudate it is called *organization* (as in organizing pneumonia affecting the lung).

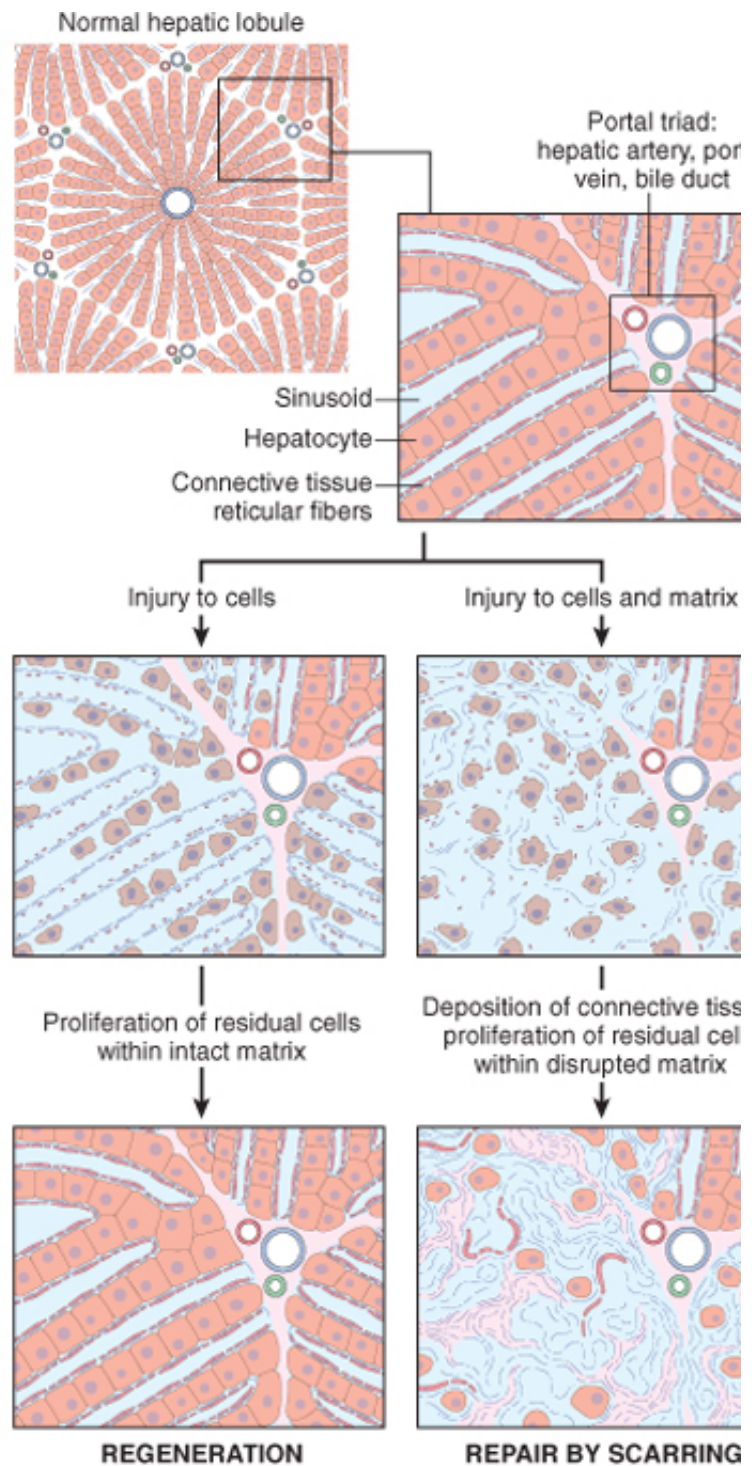
Repair involves the proliferation of various cells, and close interactions between cells and the extracellular matrix (ECM). Therefore, an understanding of the process of repair requires some knowledge of the control of cell proliferation and the functions of the ECM. In this chapter we first discuss the principles of cellular proliferation, the roles of stem cells in tissue homeostasis, and the roles of growth factors in the proliferation of different cell types involved in repair. This is followed by a discussion of some important properties of the ECM, and how it is involved in repair. These sections lay the foundation for a consideration of the salient features of regeneration and healing by scar formation, concluding with a description of cutaneous wound healing as an illustration of the repair process.







## THE CONTROL OF CELL PROLIFERATION



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Figure 3-1 Mechanisms of tissue repair. In this example, injury to the liver is repaired by regeneration if only the l

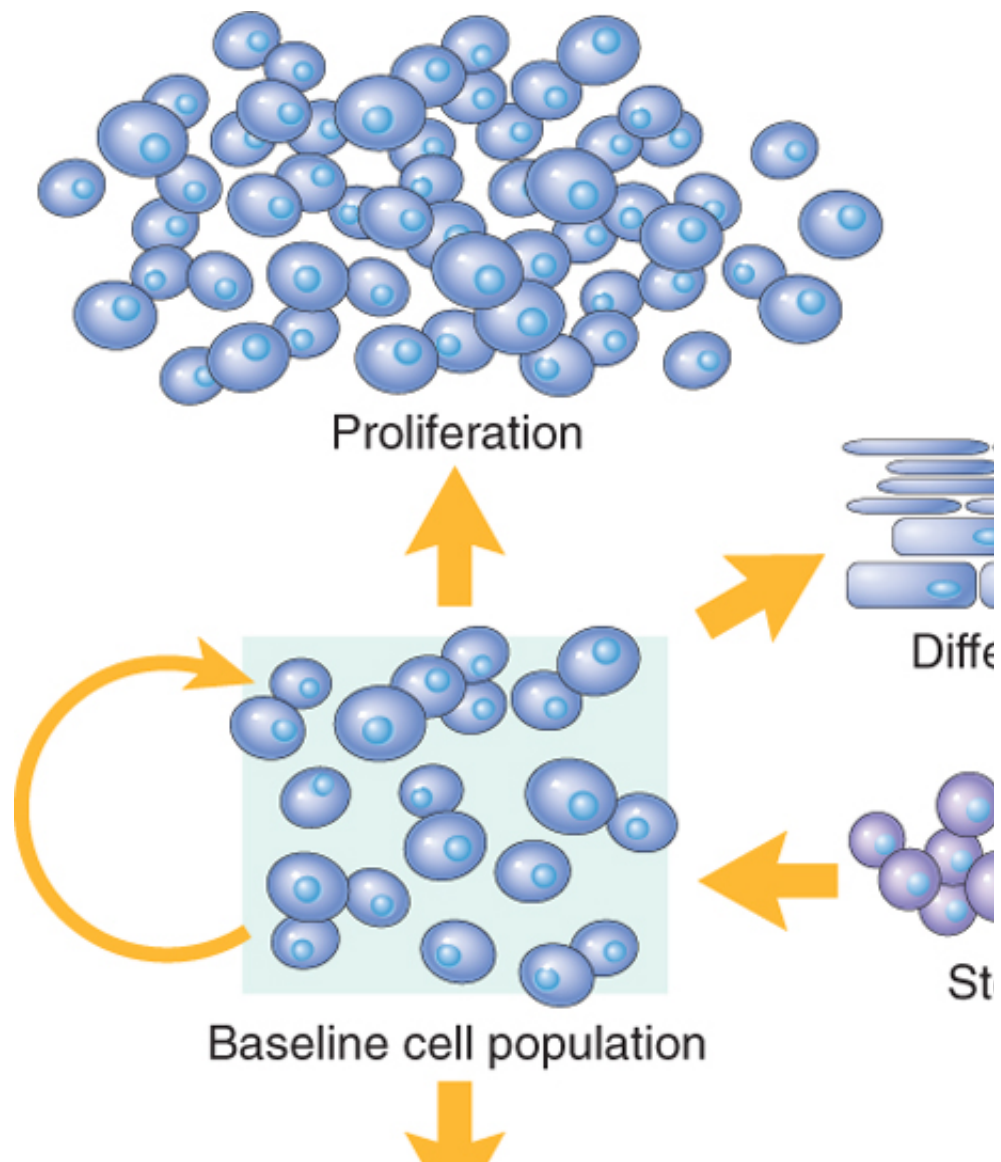
fibrous tissue if the matrix is also injured.

As we will discuss later, several cell types proliferate during tissue repair. These include the remnants of the original tissue (to restore normal structure), vascular endothelial cells (to create new vessels that provide the nutrients), and fibroblasts (the source of the fibrous tissue that forms the scar to fill defects that cannot be corrected). The proliferation of these cell types is driven by proteins that are collectively called *growth factors*. The responses of cells to these factors, and the ability of these cells to divide and expand in numbers, determine the adequacy of the repair process. In the following sections we describe the regulation of cell proliferation and growth factors.

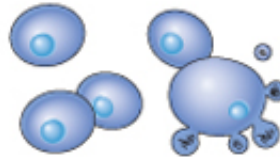
The normal size of cell populations is determined by a balance of cell proliferation, cell death, and differentiation. Differentiated cells from stem cells (Fig. 3-2). Below we first discuss cell proliferation and stem cell differentiation.

### The Cell Cycle

To understand physiologic cell proliferation (as in repair) and pathologic proliferation (as in cancer), we must understand the cell cycle and its regulation. Here we briefly summarize the main features of the cell cycle and its control. A more detailed discussion of these topics is presented in Chapter 6, in the context of neoplasia.

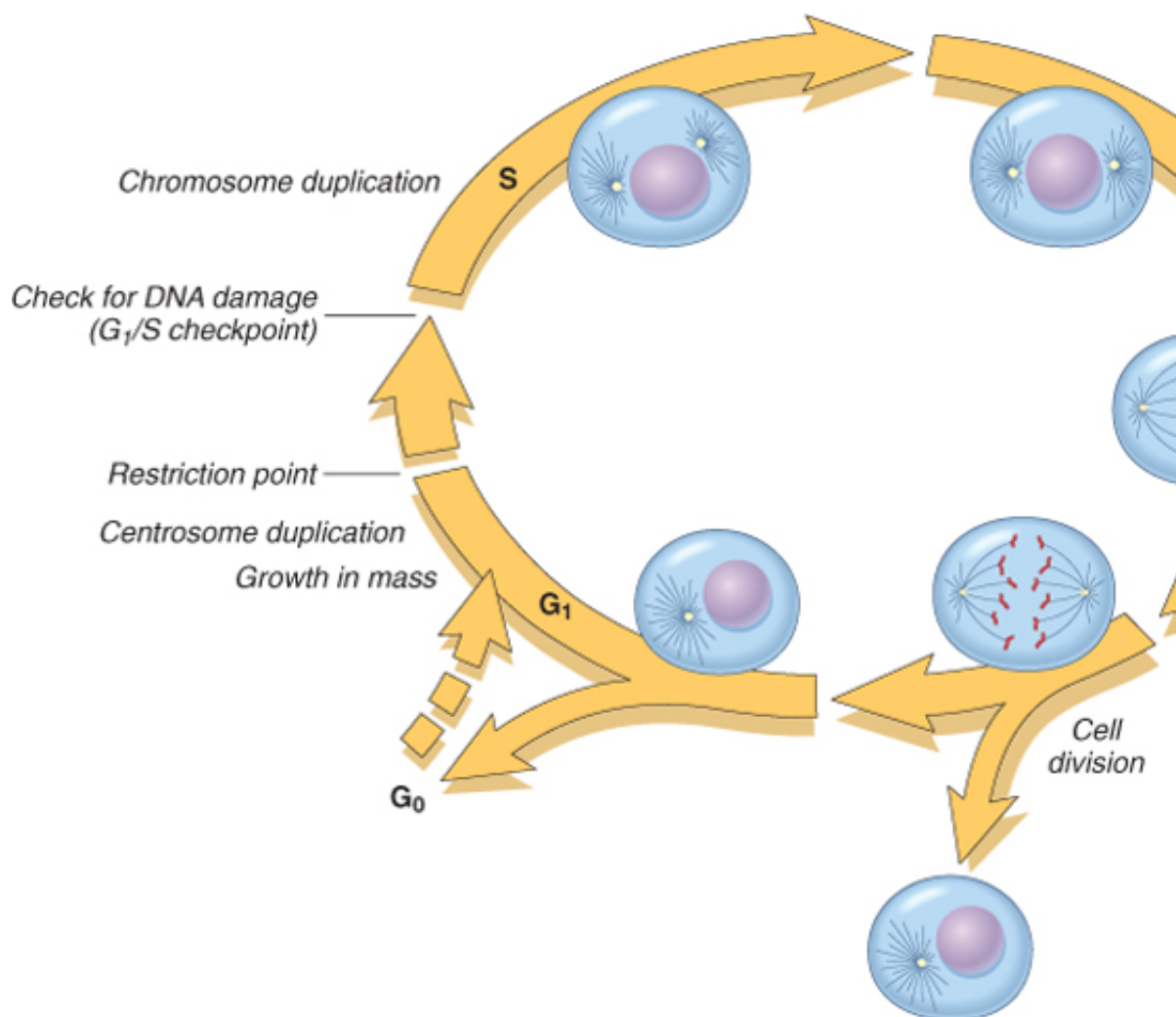


## Cell death (apoptosis)



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Figure 3-2 Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of proliferation or differentiation. (Modified from McCarthy NJ, et al: Apoptosis in the development and cancer. *Cancer Metastasis Rev* 11:157, 1992.)



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Figure 3-3 Cell populations and cycle landmarks. Note the cell cycle stages (**G<sub>0</sub>**, **G<sub>1</sub>**, **S**, **G<sub>2</sub>** and **M**), the **G<sub>1</sub>** restriction point. While some cell populations continuously cycle and proliferate (e.g., epidermis, GI epithelium), others are quiescent (e.g., hepatocytes); permanent cells (e.g., neurons and cardiac myocytes) do not have the capacity to proliferate (see text). (Philadelphia, WB Saunders, 2002.)

The key processes in the proliferation of cells are DNA replication and mitosis. The sequence of events

The key processes in the proliferation of cells are DNA replication and mitosis. The sequence of events is known as the *cell cycle*. The cell cycle consists of a series of steps at which the cell checks for the ability to proceed to the next step (Fig. 3-3). Because of its central role in growth regulation, the cell cycle is both positive and negative. The cycle consists of the presynthetic growth phase 1 ( $G_1$ ), the DNA synthesis phase ( $G_2$ ), and the mitotic phase ( $M$ ). Non-dividing cells are either in cell cycle arrest in  $G_1$  or they exit the cycle. A stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the entry into the first, i.e.  $G_1$ , phase of the cycle. Further progression is determined by the ability of the cell to maintain a mechanism for cell integrity, known as *checkpoint control*. Checkpoint controls prevent DNA replication either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells. Entry into the cell cycle from  $G_1$  is regulated by proteins called *cyclins*, which form complexes with enzymes called *CDKs*. CDKs work by promoting DNA replication and various aspects of the mitotic process and are required for progression through  $G_2$  and mitosis. CDK activity is suppressed during  $G_1$  by multiple mechanisms (Chapter 6). As we shall see below, a major action of checkpoint controls is by releasing the suppression of CDK activity. Once cells enter the S phase, the cell cycle progresses through  $G_2$  and mitosis.

### Proliferative Capacities of Tissues

The ability of tissues to repair themselves is critically influenced by their intrinsic proliferative capacities. The tissues of the body are divided into three groups.

#### Continuously Dividing Tissues

Cells of these tissues (also known as *labile tissues*) are continuously being lost and replaced by the proliferation of mature cells. Labile cells include hematopoietic cells in the bone marrow and the cells of the stratified squamous surfaces of the skin, oral cavity, vagina, and cervix; the cuboidal epithelia of the salivary glands, pancreas, biliary tract; the columnar epithelium of the gastrointestinal tract, uterine endometrium, and epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the proliferative capacity is intact.

#### Stable Tissues

Cells of these tissues are quiescent (in the  $G_0$  stage of the cell cycle) and have only minimal replication. However, these cells are capable of proliferating in response to injury or loss of tissue mass. Stable tissues include most solid tissues, such as liver, kidney, and pancreas. They also include endothelial cells, fibroblasts, and smooth muscle cells. Proliferation of these cells is particularly important in wound healing. With the exception of liver, stable tissues regenerate after injury.

#### Permanent Tissues

The cells of these tissues are considered to be terminally differentiated and nonproliferative in postnatal life. Cardiac muscle cells belong to this category. Thus, injury to brain or heart is irreversible and results in the death of myocytes. Limited stem cell replication and differentiation occurs in some areas of the brain and heart that heart muscle cells may proliferate after myocardial necrosis. Nevertheless, whatever proliferation is insufficient to produce tissue regeneration after injury. Skeletal muscle is usually classified as a permanent tissue. Attached to the endomysial sheath provide some regenerative capacity for this tissue. In permanent tissues, scar formation is common.

With the exception of tissues composed primarily of nondividing permanent cells (e.g., cardiac muscle), most tissues contain variable proportions of three cell types: continuously dividing cells, quiescent cells that can proliferate, and terminally differentiated cells.

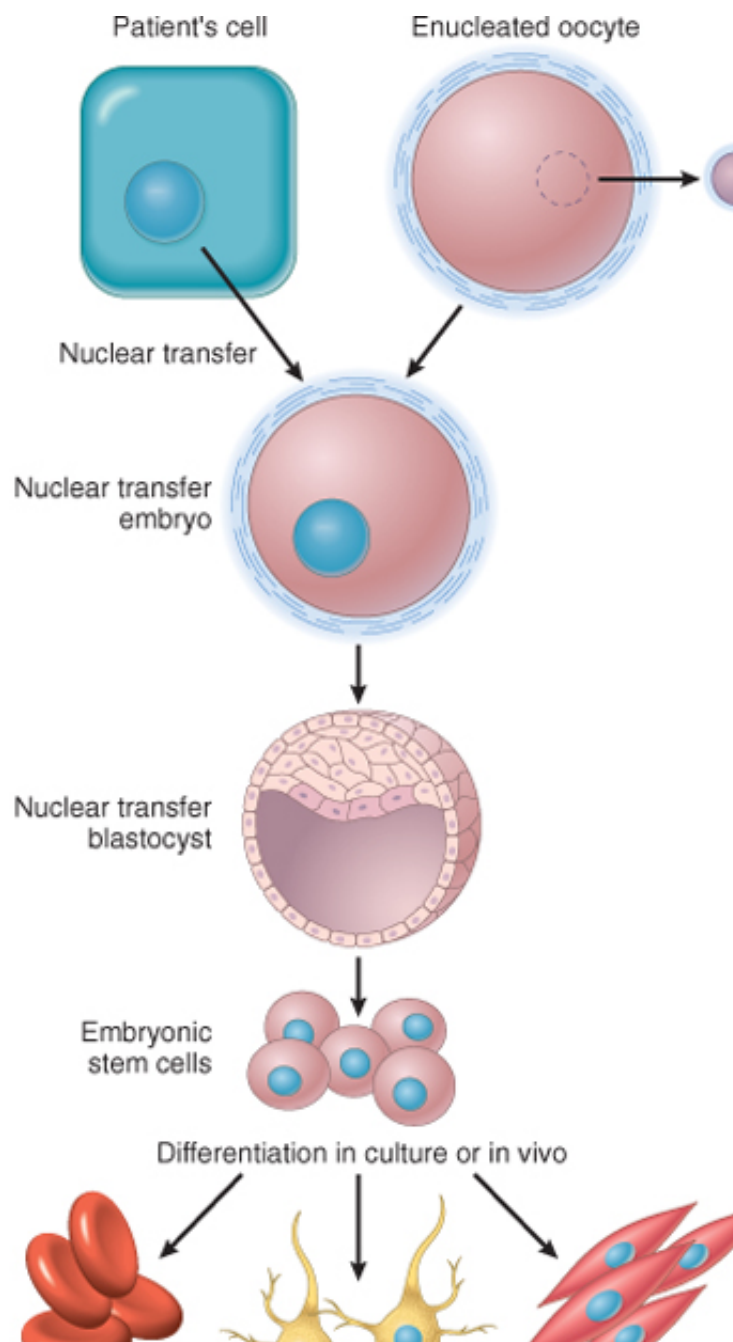
### Stem Cells

In most continuously dividing tissues the mature cells are terminally differentiated and short-lived. They are replenished by the differentiation of cells generated from stem cells. Thus, in these tissues there is a balance between the replication and differentiation of stem cells and the death of the mature, fully differentiated cells. Stem cells are found in the multilayered epithelium of the skin and the gastrointestinal tract, in which stem cell niches have been identified. Cells differentiate progressively as they migrate to the upper layers of the epithelium and are eventually shed from the surface of the tissue.



from the surface of the tissue.

*Stem cells are characterized by two important properties: self-renewal capacity and asymmetric re* cells means that after each cell division, some progeny enter a differentiation pathway, while other self-renewal capacity. Stem cells with the capacity to generate multiple cell lineages (*pluripotent s* and are called *embryonic stem (ES) cells*. As mentioned above, stem cells are normally present in lineages specific for the tissue. However, it is now recognized that stem cells with the capacity to the bone marrow and several other tissues of adult individuals. These cells are called *tissue stem* stem cells have similar differentiation capacity (referred to as *differentiation plasticity*) as ES cells and much dispute. *Bone marrow stem cells* have very broad differentiation capabilities, being able endothelium, and muscle. This developmental plasticity was first interpreted as being the consequ change in the differentiation program of an already committed cell. Most likely, however, developr specific pathway from the many differentiation pathways available to uncommitted progenitor cells





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Figure 3-4 Steps involved in therapeutic cloning using embryonic stem (ES) cells for cell therapy. In this procedure, a patient's somatic cell is introduced into an enucleated oocyte. The oocyte is activated, and the zygote divides to become a blastocyst containing ES cells; these cells are capable of differentiating into various tissues, either in culture or after transplantation. The ES cells can be used to reconstitute or repopulate damaged organs from a patient using the cells of the patient, thus avoiding immunologic rejection. Jaenisch R: Nuclear transplantation, embryonic stem cells, and the potential for cell therapy. N Engl J Med 349: 1284-1292, 2003. Medical Society. Adapted with permission 2006. All rights reserved.

The new field of *regenerative medicine* has as its main goal the regeneration and repopulation of cells. One of the most exciting prospects in this field is the type of stem cell therapy known as *cell therapy*. The procedures are illustrated in Figure 3-4. Other potential therapeutic strategies using stem cells involve the use of stem cells to treat injury, mobilization of stem cells from the bone marrow into injured tissue, and the use of stem cell-derived amounts of differentiated cells for transplantation into injured tissue.

## SUMMARY

**Cell Proliferation, the Cell Cycle, and Stem Cells** Cell proliferation is regulated by a complex of cyclin-dependent kinases (CDKs), which regulate the phosphorylation of proteins that control cell cycle progression leading to DNA replication and mitosis. The cell cycle is regulated by a variety of stimulators and inhibitors, and contains intrinsic checkpoint controls to prevent errors. Tissues are divided into labile, stable and permanent, according to the turnover of their cells. Continuously dividing tissues (labile tissues) contain stem cells that replace lost cells and maintain tissue homeostasis.





## THE NATURE AND MECHANISMS OF ACTION OF GROWTH FACTORS

Cell proliferation can be triggered by many chemical mediators, such as growth factors, hormones, and cytokines. Although hormones and many cytokines are involved in the stimulation or inhibition of cell growth, they have many other functions and are traditionally discussed separately (they are alluded to in various sections of this book). Signals from the ECM are also important inducers of cell replication, and they will be discussed later. In this section, we focus on *polypeptide growth factors*, whose major role is to promote cell survival and proliferation and which are important in regeneration and healing.

*Expansion of cell populations usually involves an increase in cell size (growth), cell division (mitosis), and protection from apoptotic death (survival).* Strictly speaking, the term "growth factors" should be used for proteins that increase cell size, and "mitogens" and "survival factor" should be used for molecules with the other activities. However, many growth factors have all these activities, and by convention "growth factor" is used for a protein that expands cell populations by stimulating cell division (usually accompanied by increased cell size) and by promoting cell survival.

Most growth factors have pleiotropic effects; that is, in addition to stimulating cellular proliferation, they stimulate migration, differentiation and contractility, and enhance the synthesis of specialized proteins (such as collagen in fibroblasts). A growth factor may act on a specific cell type or on multiple cell types. They induce cell proliferation by binding to specific receptors and affecting the expression of genes whose products typically have several functions—they relieve blocks on cell cycle progression (thus promoting replication), they prevent apoptosis, and they enhance the synthesis of cellular proteins in preparation for mitosis. A major activity of growth factors is to stimulate the function of growth control genes, many of which are called *protooncogenes* because mutations in them lead to unrestrained cell proliferation characteristic of cancer (oncogenesis) ([Chapter 6](#)). Some growth factors stimulate proliferation of some cells and inhibit cycling of other cells. In fact, a growth factor can have opposite effects on the same cell depending on its concentration. An example of such a growth factor is transforming growth factor- $\beta$  (TGF- $\beta$ ).

There is a huge (and ever-increasing) list of known growth factors. Rather than attempt an exhaustive cataloguing, we will highlight only selected molecules that contribute to tissue repair ([Table 3-1](#)). Many of the growth factors that are involved in repair are produced by leukocytes that are recruited to the site of injury or are activated at this site, as part of the inflammatory process. Other growth factors are produced by the parenchymal cells or the stromal (connective tissue) cells in response to cell injury or loss. Below we discuss general principles of how these growth factors work. We return to the roles of individual growth factors in the repair process later in the chapter.

### Signaling Mechanisms of Growth Factor Receptors

The major intracellular signaling pathways induced by growth factor receptors are similar to those of many other cellular receptors that recognize extracellular ligands. The binding of a ligand to its receptor triggers a series of events by which extracellular signals are transduced into the cell, leading to the stimulation or repression of gene expression. Signaling may occur directly in the same cell, between adjacent cells, or over greater distances ([Fig. 3-5](#)).

*Autocrine* signaling, in which a substance acts predominantly (or even exclusively) on the cell that secretes it. This pathway is important in the immune response (e.g. lymphocyte proliferation induced by some cytokines) and in compensatory epithelial hyperplasia (e.g., liver regeneration). *Paracrine* signaling, in which a substance affects

cells in the immediate vicinity of the cell that released the agent. This pathway is important for recruiting inflammatory cells to the site of infection ([Chapter 2](#)), and for wound healing. *Endocrine* signaling, in which a regulatory substance, such as a hormone, is released into the bloodstream and acts on target cells at a distance.

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**Table 3-1. Growth Factors and Cytokines Involved in Regeneration and Wound Healing**

Cytokine	Symbol	Source	Functions
Epidermal growth factor	EGF	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor $\alpha$	TGF- $\alpha$	Activated macrophages, T lymphocytes, keratinocytes, and many other cells	Similar to EGF; stimulates replication of hepatocytes and many epithelial cells
Hepatocyte growth factor (scatter factor)	HGF	Mesenchymal cells	Enhances proliferation of epithelial and endothelial cells, and of hepatocytes; increases cell motility
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells (see text)
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound remodeling; regulates integrin expression
Fibroblast growth factor 1 (acidic), -2 (basic), and family	FGF-1, -2	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts, and many tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Transforming growth factor $\beta$ (isoforms 1, 2, 3)	TGF- $\beta$	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; regulates integrin expression and other cytokines
Keratinocyte growth factor (FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

HA, Hyaluronic acid; MMPs, matrix metalloproteinase; PMNs, polymorphonuclear cells; TIMP, tissue inhibitor of matrix metalloproteinase.

Modified from Schwartz SI: Principles of Surgery. McGraw Hill, New York, 1999.

Receptor proteins are generally located on the cell surface, but they may be intracellular; in the latter case, the ligands must be sufficiently hydrophobic to enter the cell (e.g., vitamin D,



or steroid and thyroid hormones). *The binding of a ligand to its cell surface receptor leads to a cascade of secondary intracellular events that culminate in transcription factor activation or repression, leading to cellular responses.* For some intracellular receptors, ligand binding leads to the formation of receptor-ligand complexes that directly associate with nuclear DNA and activate or turn off gene transcription. In some cases, cytoplasmic transcription factors called STATs (discussed later) migrate into the nucleus and bind to DNA directly. Regardless of their origin, transcription factors bind to gene promoters and enhancers to trigger or inhibit transcription.

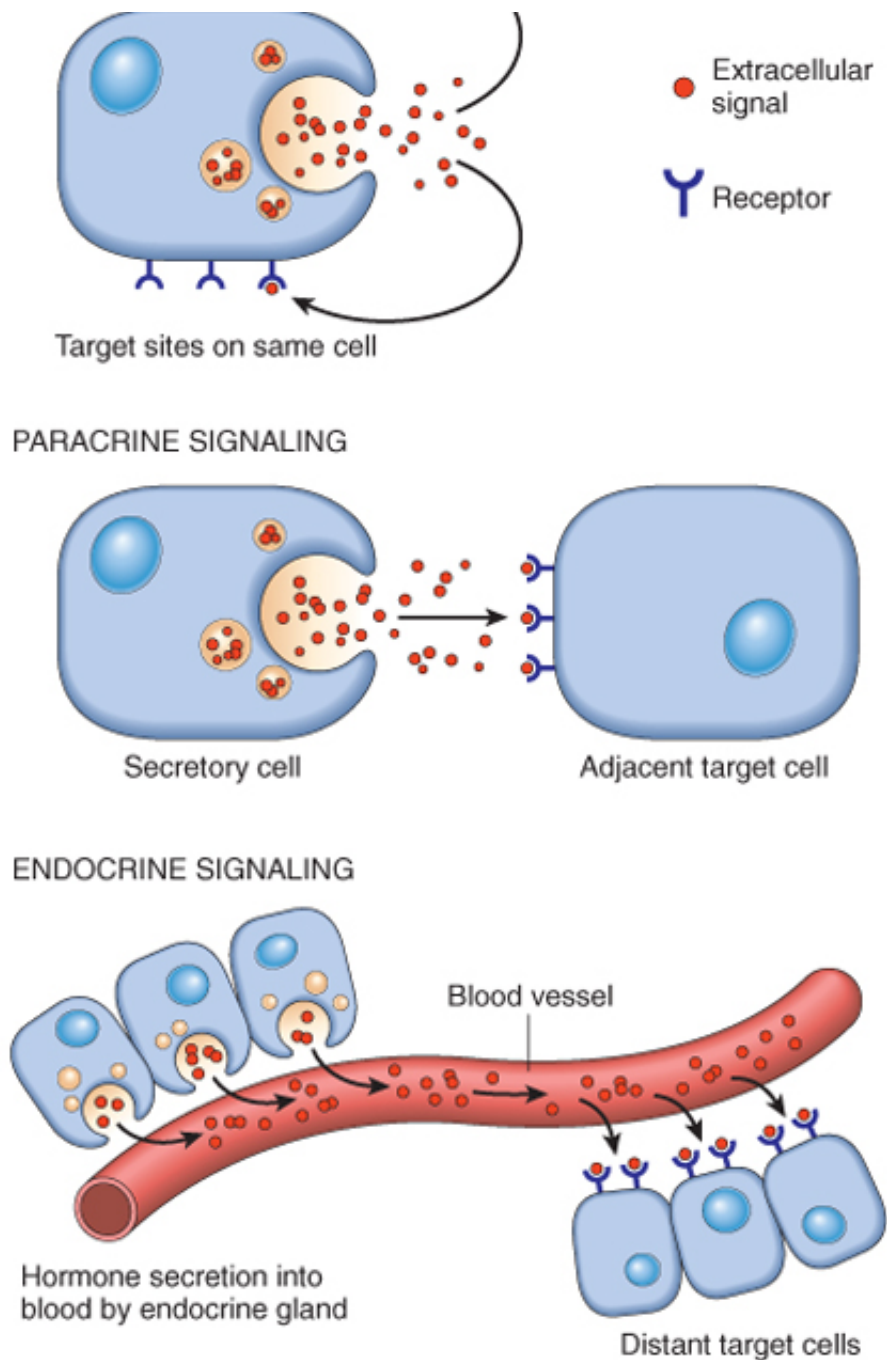
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Figure 3-6 presents an overview of signal transduction originating from three types of receptors: receptors with tyrosine kinase activity, G-protein-coupled receptors, and receptors without intrinsic enzymatic activity:

*Receptors with intrinsic kinase activity.* These are usually dimeric transmembrane molecules with an extracellular ligand-binding domain; ligand binding causes stable dimerization with subsequent phosphorylation of the receptor subunits. Once phosphorylated, the receptors can activate other intracellular proteins (e.g., RAS, phosphatidylinositol 3-[PI3] kinase, phospholipase C $\gamma$  [PLC- $\gamma$ ]) and stimulate a cascade of events leading to entry into the cell cycle and cell cycle progression, or induction of other transcriptional programs. An especially important pathway stimulated by RAS activation is the *mitogen-activated protein (MAP) kinase cascade*, which is involved in the intracellular signaling of many growth factors, including *epidermal growth factor (EGF)*, *vascular endothelial growth factor (VEGF)*, *fibroblast growth factor (FGF)*, and *hepatocyte growth factor (HGF)*. *G-protein-coupled receptors.* These receptors contain seven transmembrane  $\alpha$ -helix segments and are also known as *seven transmembrane G-protein-coupled receptors*. After ligand binding, the receptors associate with intracellular guanosine triphosphate (GTP)-binding proteins (G proteins) that contain guanosine diphosphate (GDP). Binding of the G proteins causes the exchange of GDP with GTP, resulting in activation of the proteins. Among the several transduction pathways activated through G-protein-coupled receptors are those involving *cyclic AMP (cAMP)*, and the generation of *inositol-1,4,5,-triphosphate (IP<sub>3</sub>)*, which releases calcium from the endoplasmic reticulum. Receptors in this category constitute the largest family of plasma membrane receptors (more than 1500 members have been identified) and include those for *epinephrine<sub>R</sub>*, *vasopressin<sub>R</sub>*, serotonin, histamine, and glucagon, as well as the chemokines (Chapter 2). *Receptors without intrinsic enzymatic activity.* These are usually monomeric transmembrane molecules with an extracellular ligand-binding domain; ligand interaction induces an intracellular conformational change that allows association with intracellular protein kinases called *Janus kinases (JAKs)*. Phosphorylation of JAKs activates cytoplasmic transcription factors called *STATs (signal transducers and activators of transcription)*, which shuttle directly into the nucleus. Ligands for these receptors include many cytokines, the interferons, colony-stimulating factors, growth hormone, and erythropoietin.

Note that not all ligands induce stimulatory signals; in fact, growth-inhibitory signals inducing direct inhibition or inhibition caused by cell-cell contact (*contact inhibition*) are equally important. For instance, the TGF- $\beta$  receptor has intrinsic kinase activity, and when in complex with TGF- $\beta$  it phosphorylates specific intracellular proteins, which in turn increase the synthesis of CDK inhibitors and block the activity of transcription factors and cell cycle progression.





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 Figure 3-5 Patterns of extracellular signaling, demonstrating autocrine, paracrine, and endocrine signaling (see text). (Modified from Lodish, et al [eds]: Molecular Cell Biology, 3rd ed. New York, WH Freeman, 1995.)

## SUMMARY

### Growth Factors, Receptors and Signal

**Transduction** Polypeptide growth factors act in autocrine, paracrine, or endocrine manner. Growth factors are produced transiently in response to an external stimulus and act by binding to cellular receptors. Different classes of growth factor receptors include receptors with intrinsic kinase activity, G-protein-coupled receptors and receptors without intrinsic kinase activity. Growth factors such as EGF and HGF bind to receptors with intrinsic

kinase activity, and trigger a cascade of phosphorylating events through MAP kinases, which culminate in transcription factor activation and DNA replication. Cytokines generally bind to receptors without kinase activity; such receptors interact with cytoplasmic transcription factors that move into the nucleus. Most growth factors have multiple effects, such as cell migration, differentiation, stimulation of angiogenesis and fibrogenesis in addition to cell proliferation.





## EXTRACELLULAR MATRIX (ECM) AND CELL-MATRIX INTERACTIONS

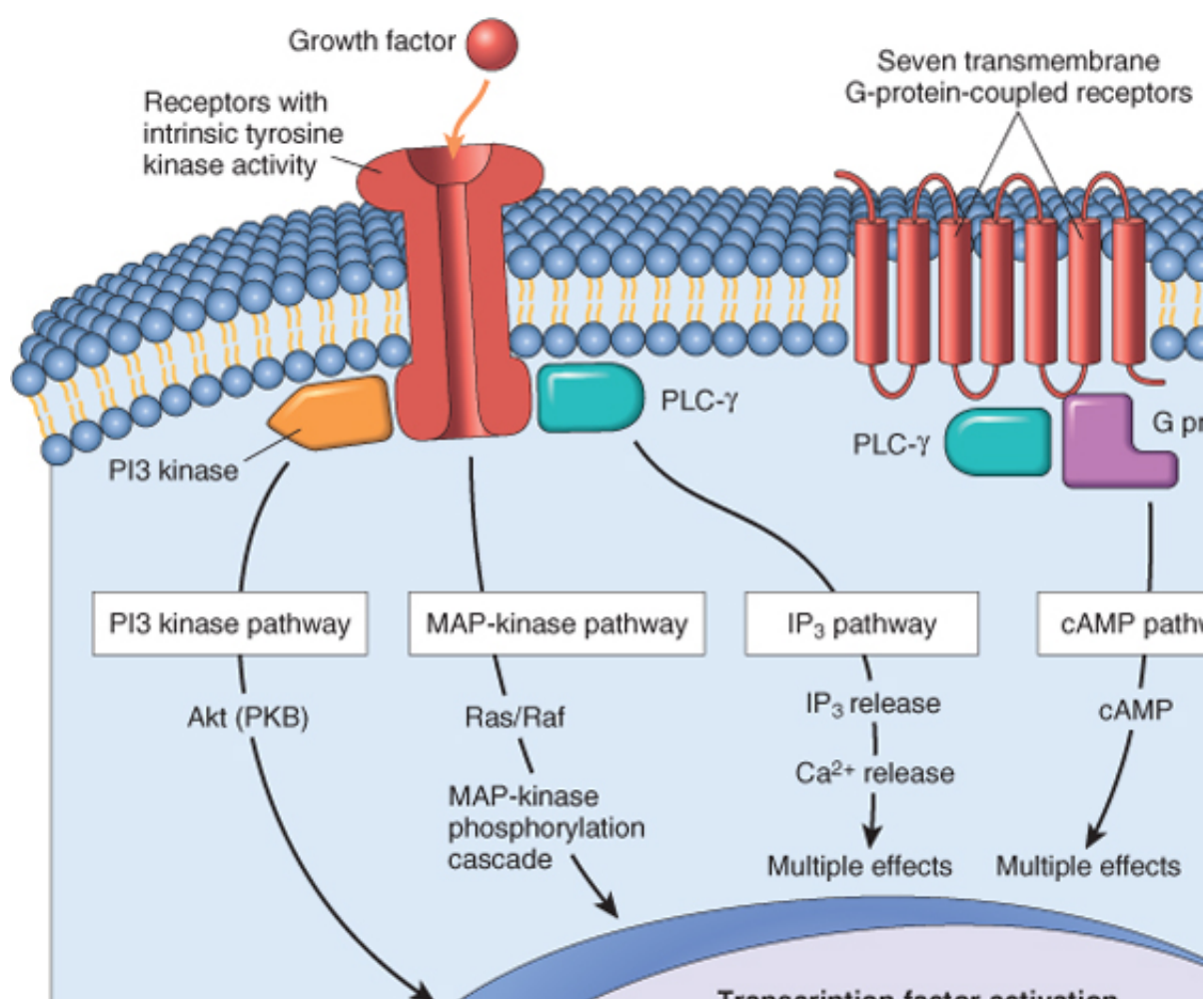
Tissue repair depends not only on growth factor activity but also on interactions between cells and *dynamic, constantly remodeling* macromolecular complex synthesized locally, which assembles in and constitutes a significant proportion of any tissue. ECM sequesters water, providing turgor to soft tissue and bone. By supplying a substratum for cell adhesion and serving as a reservoir for growth factors, ECM influences the *movement, and differentiation of the cells living within it*. Synthesis and degradation of ECM accompany chronic fibrotic processes, and tumor invasion and metastasis.

ECM occurs in two basic forms: *interstitial matrix* and *basement membrane* (Fig. 3-7).

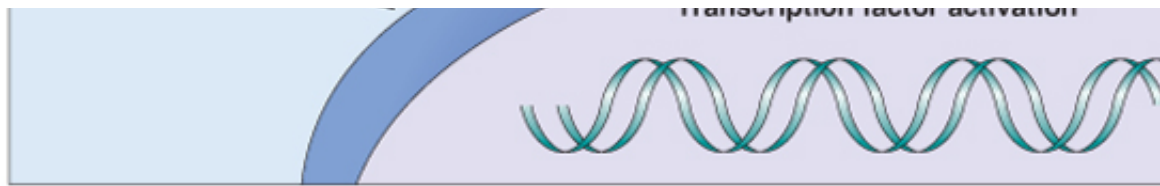
### Interstitial Matrix

This is present in the spaces between cells in connective tissue, and between epithelium and supporting structures; it is synthesized by mesenchymal cells (e.g., fibroblasts) and tends to form a three-dimensional network. Its constituents are fibrillar and nonfibrillar collagens, as well as fibronectin, elastin, proteoglycans, and hyaluronic acid (to be discussed later).

### Basement Membrane







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Figure 3-6 An overview of the major types of cell surface receptors and their principal signal transduction pathways (text). Shown are receptors with intrinsic tyrosine kinase activity, seven transmembrane G-protein-coupled receptor activity. cAMP, Cyclic adenosine<sub>3'</sub>, monophosphate; IP<sub>3</sub>, inositol triphosphate; JAK, Janus kinase; MAP kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B (also known as Akt); PLC-γ, phospholipase Cγ; STAT, sig

The seemingly random array of interstitial matrix in connective tissues becomes highly organized and smooth muscle cells, forming the specialized basement membrane. The basement membrane synthesized by overlying epithelium and underlying mesenchymal cells; it tends to form a platelike constituents are amorphous nonfibrillar type IV collagen and laminin (see later).

### Roles of the Extracellular Matrix

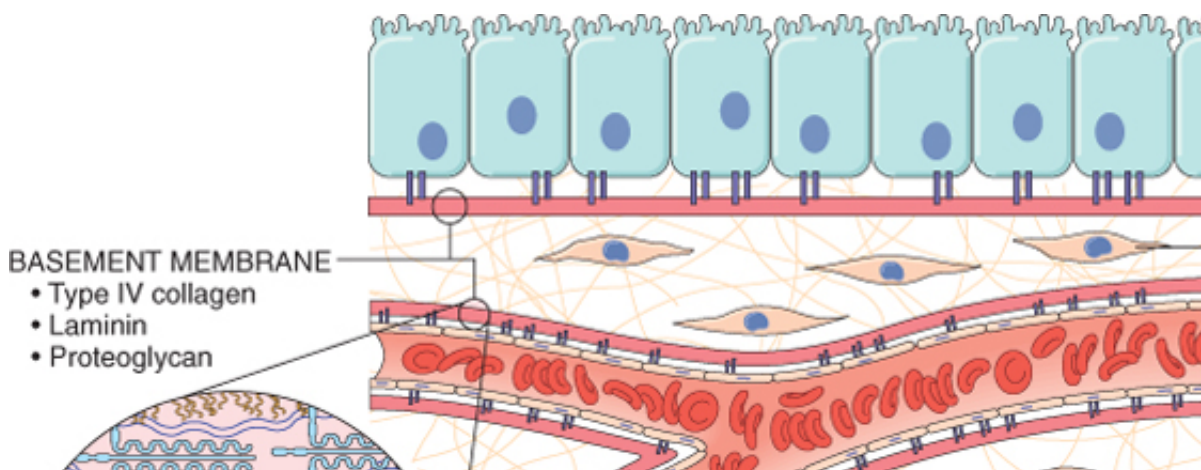
The ECM is much more than a space filler around cells. Its various functions include:

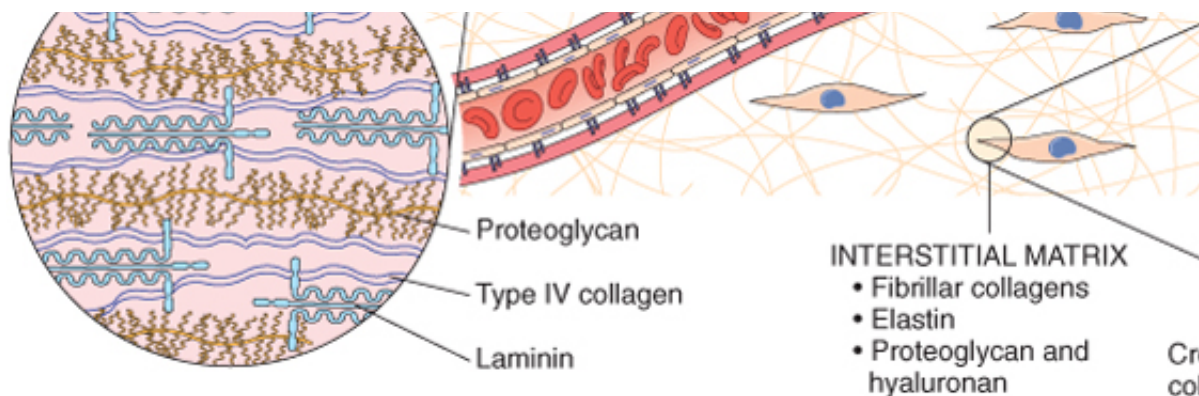
*Mechanical support* for cell anchorage and cell migration, and maintenance of cell polarity (can regulate cell proliferation by signaling through cellular receptors of the integrin family). A type of ECM proteins can affect the degree of differentiation of the cells in the tissue, also integrins. *Scaffolding for tissue renewal*. The maintenance of normal tissue structure requires scaffold. The integrity of the basement membrane or the stroma of the parenchymal cells is tissues. It is particularly noteworthy that although labile and stable cells are capable of regrowth, restitution of the normal structure only if the ECM is not damaged. Disruption of these structures leads to scar formation (see Fig. 3-1). *Establishment of tissue microenvironments*. Basement membrane separates epithelium and underlying connective tissue and also forms part of the filtration apparatus in glomeruli. *Regulatory molecules*. For example, growth factors like FGF and HGF are excreted and stored in the ECM, which allows the rapid deployment of growth factors after local injury, or during regeneration.

### Components of the Extracellular Matrix

There are three basic components of ECM: (1) fibrous structural proteins such as collagens and elastin; (2) water-hydrated gels such as proteoglycans and hyaluronan<sub>3'</sub>, which permit resilience and elasticity; (3) glycoproteins that connect the matrix elements to one another and to cells (see Fig. 3-7).

Collagen





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Figure 3-7 The major components of the extracellular matrix (ECM), including collagens, proteoglycans, and adhesive glycoproteins. Some overlaps in their constituents, basement membrane and interstitial ECM have different general compositions. Mesenchymal cells (e.g., fibroblasts) interact with ECM via integrins. For the sake of simplification, many ECM components are shown in blue (e.g., hyaluronan<sub>R</sub>, syndecan).

The collagens are fibrous structural proteins that confer tensile strength; without them human beings would be disconnected by neurons. Collagens are composed of three separate polypeptide chains braided into triple helices. Proteins are rich in hydroxyproline and hydroxylysine. About 30 collagen types have been identified in cells and tissues. Some collagen types (e.g., types I, II, III, and V) form *fibrils* by virtue of lateral cross-linking. Fibrillar collagens form a major proportion of the connective tissue in healing wounds and particularly in bone. Fibrillar collagens derive from their cross-linking, which is the result of covalent bonds catalyzed by lysyl oxidase, an enzyme that is dependent on vitamin C; therefore, children with ascorbate deficiency have skeletal deformities. Fibrillar collagens form the wall of basement membrane, and heal poorly. Genetic defects in these collagens cause diseases such as Ehlers-Danlos syndrome. Other collagens are nonfibrillar and may form basement membrane (type IV) or structures such as intervertebral discs (type IX) or dermal-epidermal junctions (type VII).

### Elastin

Although tensile strength is derived from the fibrillar collagens, the ability of tissues to recoil and resist stress is conferred by elastic tissue. This is especially important in the walls of large vessels (which must withstand high flow), as well as in the uterus, skin, and ligaments. Morphologically, elastic fibers consist of a central core surrounded by a meshlike network of *fibrillin* glycoprotein. Like collagens, elastins require a *glycine*<sub>R</sub> in every third amino acid, but having fewer cross-links. The fibrillin meshwork serves as a scaffold for the deposition of elastin. Defects in fibrillin synthesis lead to skeletal abnormalities and weakened aortic walls (*Marfan syndrome*; *Chagas disease*).

### Proteoglycans and Hyaluronan

Proteoglycans form highly hydrated compressible gels conferring resilience and lubrication (such as in cartilage). They consist of long polysaccharides called *glycosaminoglycans* (examples are *dermatan sulfate* and *heparan sulfate*). *Hyaluronan*<sub>R</sub>, a huge molecule composed of many disaccharide repeats without a protein core, is also a major component of the ECM. Because of its ability to bind water, it forms a viscous, gelatin-like matrix. Besides providing structural support, proteoglycans also serve as reservoirs for growth factors secreted into the ECM (e.g., FGF and HGF). Proteoglycans have roles in cell proliferation, migration, and adhesion. For example, the transmembrane protein *syndecan* is attached to *hyaluronan*<sub>R</sub> chains that can bind such matrix growth factors as FGF, facilitating the integration of the ECM with the cell (Fig. 3-8). *Syndecan* also associates with the intracellular actin cytoskeleton and thereby helps to maintain cell morphology.

### Adhesive Glycoproteins and Adhesion Receptors





*Fibronectin* is a large (450-kD) disulfide-linked heterodimer synthesized by a variety of cells, including endothelium. Fibronectin messenger RNA (mRNA) has two splice forms, which generate tissue and plasma forms. Specific domains that bind to a wide spectrum of ECM components (e.g., collagen, fibrin, heparin, to cell integrins via a tripeptide arginine-glycine-aspartic acid (abbreviated RGD) motif. Tissue fibronectin is involved in wound healing sites; plasma fibronectin binds to fibrin to form the provisional blood clot of a wound and re-epithelialization.

*Laminin* is the most abundant glycoprotein in basement membrane. It is a 820-kD cross-shaped heterotrimer that binds to underlying ECM components such as type IV collagen and heparan sulfate. Besides mediating adhesion, laminin can also modulate cell proliferation, differentiation, and motility.

*Integrins* are a family of transmembrane heterodimeric glycoproteins composed of  $\alpha$  and  $\beta$  chains. They bind to ECM components, such as fibronectins and laminins. We discussed some of the integrins as leukocyte adhesion and transmigration across endothelium at sites of inflammation, and we will meet them again in aggregation in [Chapter 4](#). Integrins are present in the plasma membrane of most animal cells, and they bind to many ECM components through RGD motifs, initiating signaling cascades that can affect cell proliferation and differentiation. Their intracellular domains link to actin filaments at focal adhesion complexes, through vinculin ([Fig. 3-9](#)). Integrin signal transduction utilizes the same intracellular signaling pathways used for growth factor receptors. For example, integrin-mediated adhesion to fibronectin can trigger elements of the MAP kinase, PI3 kinase, and JAK/STAT pathways. In this manner, extracellular mechanical forces can be coupled to intracellular synthetic and transcriptional responses.

## SUMMARY

**Extracellular Matrix and Tissue Repair** The ECM consists of: the interstitial matrix, made up of collagens and several glycoproteins; and basement membranes surrounding vessels, made up of nonfibrillar collagen and laminin. The ECM has several functions:

- It provides mechanical support to tissues; this is the role of collagens.
- It provides a substrate for cell growth and the formation of tissue microenvironment.
- It regulates cell proliferation and differentiation; proteoglycans bind growth factors and cytokines, maintaining their concentration, and fibronectin and laminin stimulate cells via cellular adhesion.

An intact ECM is required for tissue regeneration, and if the ECM is damaged, repair is accomplished by scar formation.

Having described the basic components of tissue repair, we now proceed to a discussion of repair processes.

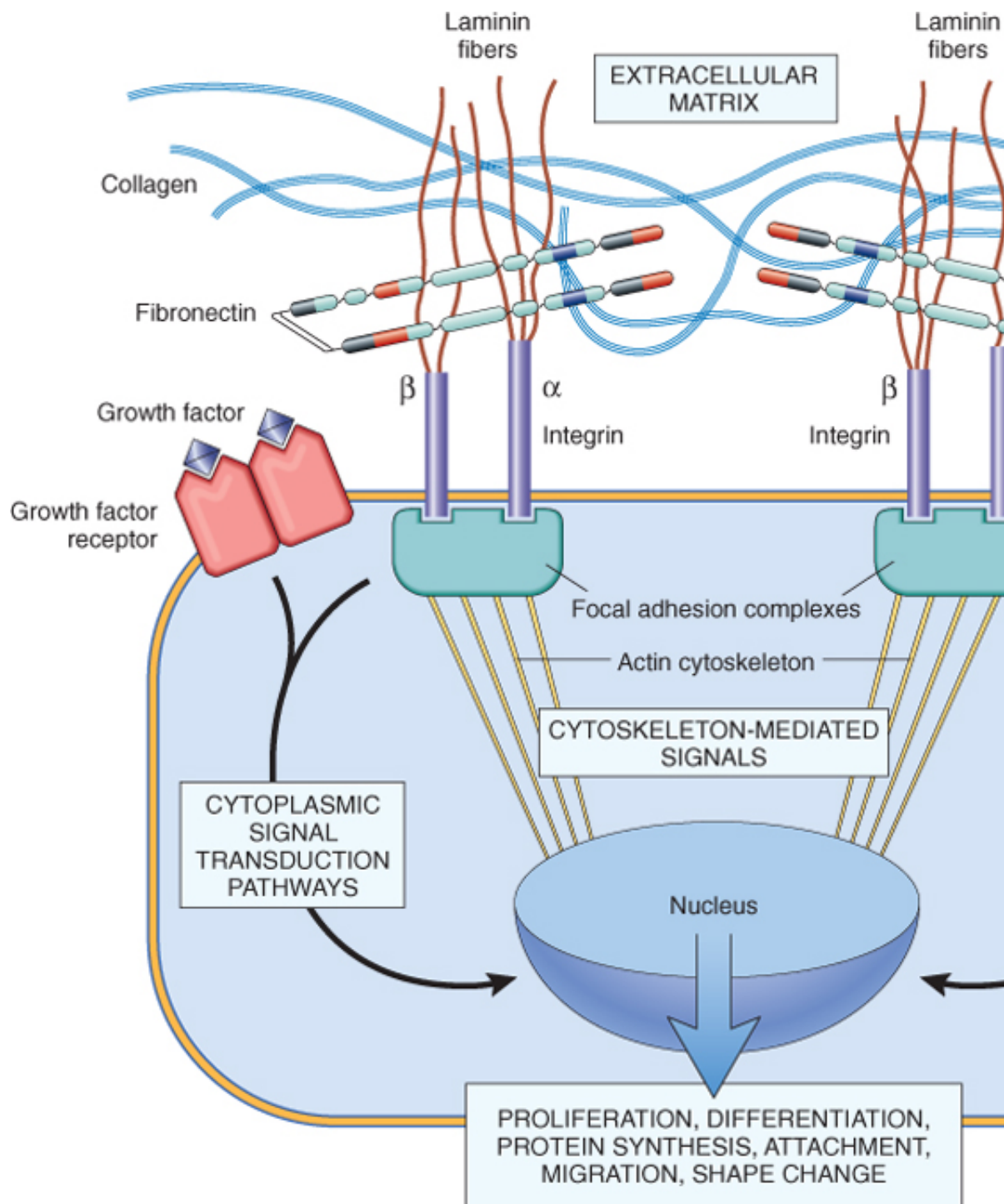


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## CELL AND TISSUE REGENERATION



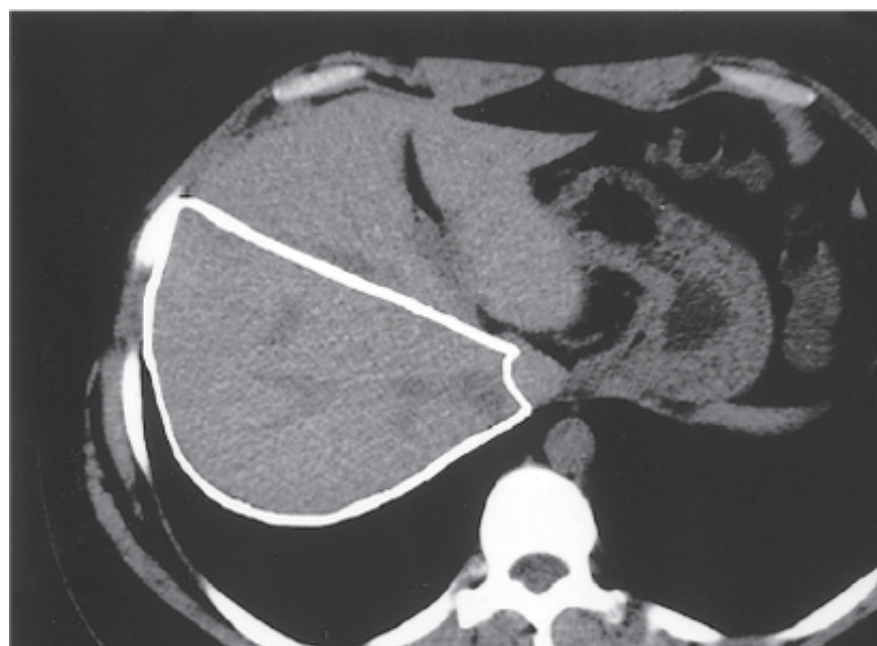
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Figure 3-9 Mechanisms by which ECM components (e.g., fibronectin and laminin) and growth factors can influence protein synthesis. Integrins bind ECM and interact with the cytoskeleton at focal adhesion complexes (protein acc

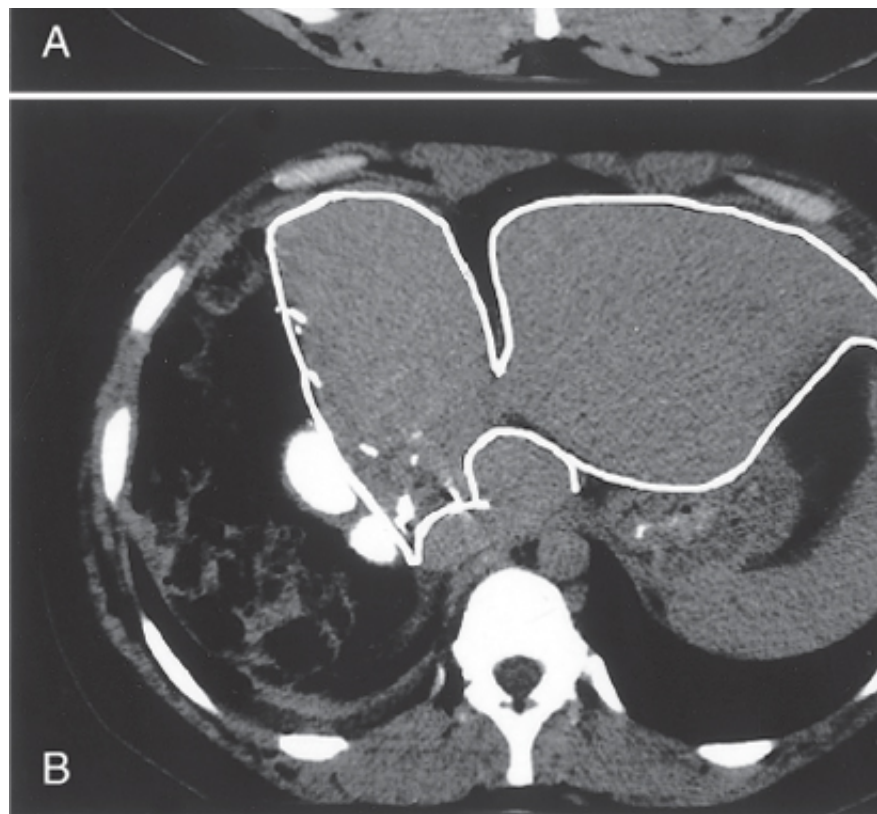
This can initiate the production of intracellular second messengers or can directly mediate nuclear signals. Cell signaling pathways that overlap with those activated by integrins. Signals received from growth factors and EC various responses, including changes in cell proliferation, locomotion, and dif

As discussed above, cell renewal occurs continuously in labile tissues, such as the bone marrow, epithelia or an increased loss of blood cells can be corrected by the proliferation and differentiation by proliferation of more differentiated progenitors. The renewal of hematopoietic cells is driven by *factors* (CSFs), which are produced in response to increased consumption or loss of blood cells. I in the renewal of labile epithelia.

Tissue regeneration can occur in parenchymal organs with stable cell populations, but with the ex limited process. Pancreas, adrenal, thyroid, and lung tissues have some regenerative capacity. TI the contralateral kidney a compensatory response that consists of both hypertrophy and hyperpla: mechanisms underlying this response are not understood. Much more dramatic, however, is the r occurs after surgical removal of hepatic tissue. As much as 40% to 60% of the liver may be remov transplantation, in which a portion of the liver is resected from a normal individual and is transplan disease (Fig. 3-10), or after partial hepatectomies performed for tumor removal. In all of these situ proliferative response of the remaining hepatocytes (which are normally quiescent), and the subs nonparenchymal cells. In experimental systems, hepatocyte replication after partial hepatectomy i necrosis factor [TNF] and interleukin 6 [IL-6]) that "prime" the cells for replication by stimulating th cycle. Progression through the cell cycle is dependent on the activity of growth factors such as *HG includes transforming growth factor  $\alpha$* .

*HGF* is produced by fibroblasts, endothelial cells, and liver nonparenchymal cells. It induce epithelial cells, including those in the skin, mammary gland, and lungs. *HGF* binds to a spe which is frequently overexpressed in human cancers. *EGF* and *TGF- $\alpha$*  share a common rec or EGFR) with intrinsic tyrosine kinase activity. The "EGFR" is actually a family of receptor: ligands of the EGF family. *EGF/TGF- $\alpha$*  is mitogenic for hepatocytes and most epithelial cell wound healing *EGF* is produced by keratinocytes, macrophages, and other inflammatory c EGFR1 or ERB B1) is frequently overexpressed in lung and some brain tumors and is an ir treatment of these conditions. ERB B2 (also known as HER-2/NEU) has received great att breast cancers, in which it is a target for effective cancer control (discussed in Chapter 6).





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 Figure 3-10 Regeneration of human liver. Computed tomography scans of the donor liver in living-donor liver transplantation. Note the right lobe (*outline*), which will be resected and used as a transplant. **B**, Scan of the same liver showing enlargement of the left lobe (*outline*) without regrowth of the right lobe. (Courtesy of R. Troisi, MD, GI)

It should be emphasized that extensive regeneration or compensatory hyperplasia can occur only if the tissue is functionally intact, as after partial surgical resection. By contrast, if the tissue is damaged by infection, inflammation, and is accompanied by scarring.



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## REPAIR BY CONNECTIVE TISSUE

If tissue injury is severe or chronic, and results in damage to parenchymal cells and epithelia as well as nondividing cells are injured, repair cannot be accomplished by regeneration alone. Under these conditions, repair is accomplished by the replacement of the nonregenerated cells with connective tissue, or by a combination of regeneration of some cells and replacement of the rest with connective tissue.

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast proliferation. By 3 to 5 days, a specialized type of tissue that is characteristic of healing, called *granulation tissue*, is formed. It derives from the pink, soft, granular gross appearance, such as that seen beneath the scab of a wound. It is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries (angiogenesis). Granulation tissue then progressively accumulates connective tissue matrix, eventually resulting in a scar, which may remodel over time.

Repair by connective tissue deposition consists of four sequential processes:

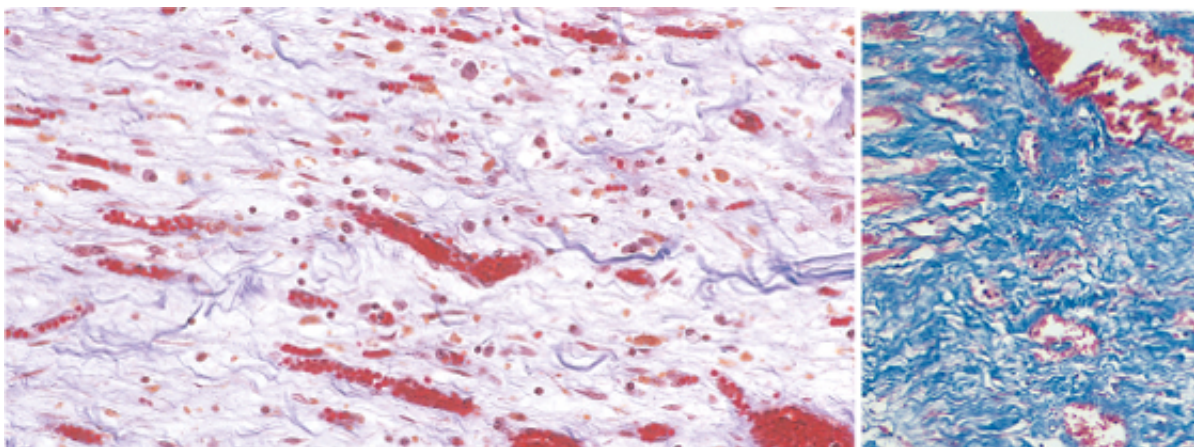
Formation of new blood vessels (*angiogenesis*)  
Migration and proliferation of fibroblasts  
Deposition of extracellular matrix (*deposition*)  
Maturation and reorganization of the fibrous tissue (*remodeling*)

### Angiogenesis

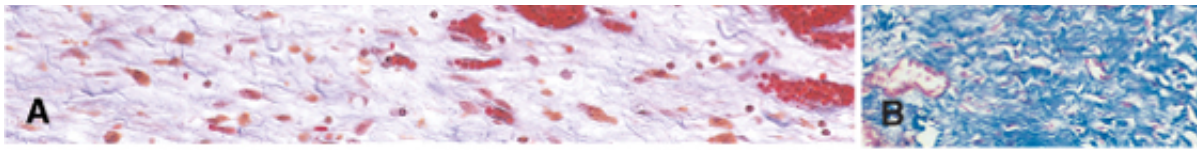
Blood vessels are assembled by two processes: *vasculogenesis*, in which the primitive vascular network (endothelial cell precursors) during embryonic development; and *angiogenesis*, or *neovascularization*, in which new blood vessels sprout out of preexisting vessels to produce new vessels (Fig. 3-12). Angiogenesis is a critical process in healing of wounds, in the development of collateral circulations at sites of ischemia, and in allowing tumors to increase in size beyond the limits of their blood supply. It has recently been found that endothelial precursor cells may migrate from the bone marrow to a site of tissue injury and participate in angiogenesis at these sites. Much work has been done to understand the mechanisms underlying angiogenesis and to develop ways to augment the process (e.g., to improve blood flow to a heart ravaged by coronary atherosclerosis) and to inhibit it when it is being developed.

The main steps that occur in angiogenesis from preexisting vessels are listed below.

Vasodilation in response to [nitric oxide](#) and increased permeability of the preexisting vessels  
Release of angiogenic growth factor (VEGF)  
Migration of endothelial cells toward the area of tissue injury  
Proliferation of endothelial cells at the leading front of migrating cells  
Inhibition of endothelial cell proliferation and remodeling into periendothelial cells (pericytes for small capillaries and smooth muscle cells for larger vessels)

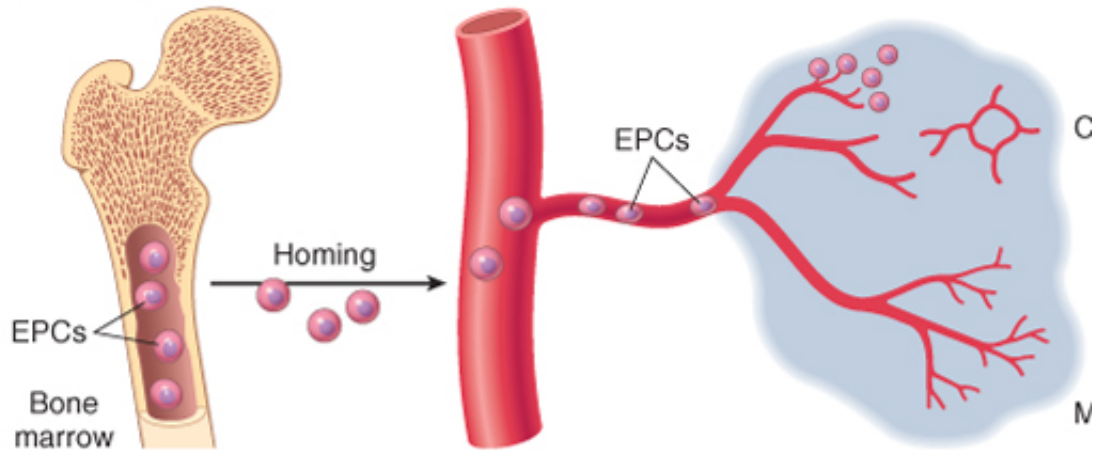




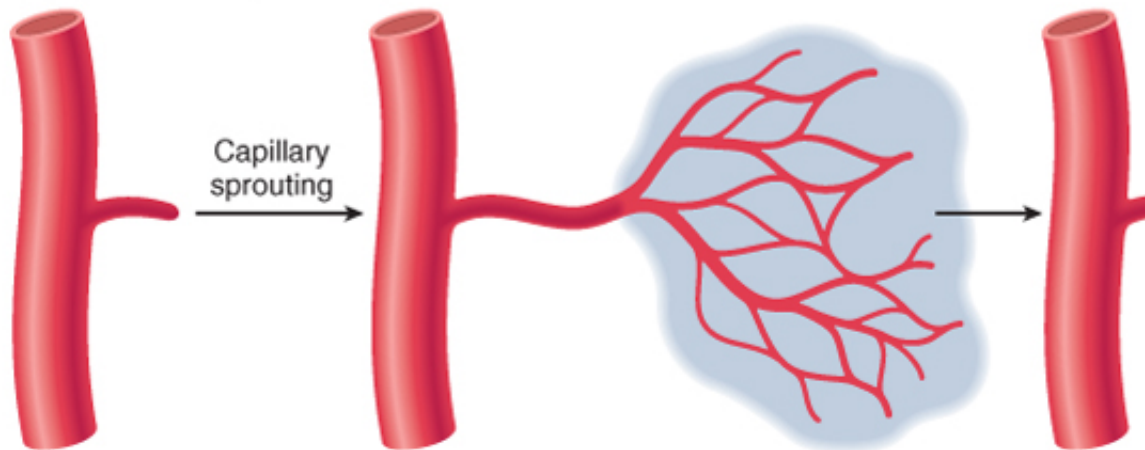


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 Figure 3-11 **A**, Granulation tissue showing numerous blood vessels, edema, and a loose ECM containing occasional the trichrome stain; minimal mature collagen can be seen at this point. **B**, Trichrome stain of mature scar, showing channels.

#### A. Angiogenesis by mobilization of EPCs from the bone marrow



#### B. Angiogenesis from preexisting vessels



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 Figure 3-12 Angiogenesis resulting from, **A**, the mobilization of bone marrow endothelial precursor cells (EPCs), and **B**, capillary sprouting from preexisting vessels. In angiogenesis from preexisting vessels, endothelial cells from these vessels become new vessels. Regardless of the mechanism of angiogenesis, vessel maturation requires the recruitment of pericytes and smooth muscle cells.  
 (Modified from Conway EM et al., Molecular mechanisms of blood vessel growth. Cardio

As mentioned, bone marrow endothelial precursor cells may also contribute to angiogenesis. The mechanism by which endothelial precursor cells located in the bone marrow migrate into sites of injury is unknown. EPCs are involved in the replacement of lost endothelial cells, in the re-endothelialization of vascular implants, in the neovascularization of ischemic tissues, and in tumor development.

New vessels formed during angiogenesis are leaky because of incompletely formed interendothelial junctions, which increases vessel permeability. This leakiness explains why granulation tissue is often edematous, may persist in healing wounds long after the acute inflammatory response has resolved. Structure of vessel sprouting in angiogenesis, largely through interactions with integrin receptors in endothelial cells, contribute to angiogenesis by destabilizing cell-ECM interactions to facilitate continued cell migration and degradation of the ECM to permit remodeling and ingrowth of vessels (e.g., *plasminogen activator*).

### *Growth Factors Involved in Angiogenesis*

Several factors induce angiogenesis, but the most important are *VEGF* and *basic fibroblast growth factor*.

VEGFs constitute a family of growth factors that include VEGF-A, -B, -C, and -D. VEGF-A is the gene that selectively regulates lymphoid vasculature. VEGFs are dimeric glycoproteins with many isoforms. The most important of VEGF:

VEGFs are expressed at low levels in most tissues and are highly expressed in kidney podocytes. They bind to a family of receptors (VEGFR-1, -2, and -3) with tyrosine kinase activity. The most important is VEGFR-2, which is restricted to endothelial cells. Targeted mutations in this receptor result in severe developmental defects. Agents can induce VEGFs, *the most important being hypoxia*. Other inducers are platelet-derived growth factor (PDGF) and TGF- $\alpha$ .

In angiogenesis originating from preexisting local vessels, VEGF stimulates both proliferation and the process of capillary sprouting. In angiogenesis involving endothelial cell precursors from the bone marrow, VEGF is required to mobilize these cells from the bone marrow and to induce proliferation and motility of these cells. Regardless of the process that leads to capillary formation, new vessels need to be stabilized by pericytes and by the deposition of connective tissue. *Angiopoietins 1 and 2* (*Ang 1* and *Ang 2*) participate in the stabilization process. In particular, Ang1 interacts with a receptor on endothelial cells. PDGF participates in the recruitment of smooth muscle cells; TGF- $\beta$  enhances the production of connective tissue.

*FGFs* constitute a family of factors with more than 20 members. The best characterized are *FGF-1* and *FGF-2*. These growth factors are produced by many cell types and bind to a family of plasma membrane receptors with tyrosine kinase activity. Released FGF can bind to heparan sulfate and be stored in the ECM. FGF-2 participates in the proliferation of endothelial cells. It also promotes the migration of macrophages and fibroblasts to the site of injury. *Keratinocyte growth factor* (*FGF-7*) may participate in enhancing the proliferation and migration of keratinocytes and may also protect the integrity of the gastrointestinal tract.

### **Migration of Fibroblasts and ECM Deposition (Scar Formation)**

*Scar formation* builds on the granulation tissue framework of new vessels and loose ECM that develops in the first two steps: (1) *migration and proliferation of fibroblasts into the site of injury* and (2) *deposition of ECM*. The stimulation of fibroblasts is driven by many growth factors, including PDGF, FGF-2 (described above), and TGF- $\beta$ . The activated endothelium, but more importantly, growth factors are also elaborated by it. In particular, are important cellular constituents of granulation tissue, and besides clearing extracellular matrix, they elaborate a host of mediators that induce fibroblast proliferation and ECM production. Sites of injury and with the appropriate chemotactic milieu lymphocytes may also be present. Each of these can stimulate fibroblast proliferation and activation.

As healing progresses, the number of proliferating fibroblasts and new vessels decreases; however, the deposition of more synthetic phenotype, and hence there is increased deposition of ECM. Collagen synthesis, which is a measure of strength in a healing wound site. As described later, collagen synthesis by fibroblasts begins early and continues for several weeks, depending on the size of the wound. As described below, many of the factors that stimulate fibroblast proliferation also participate in stimulating ECM synthesis. *Net collagen accumulation, however, depends not only on increased collagen synthesis but also on diminished collagen degradation* (discussed later). Ultimately, the granulation tissue, composed of largely inactive, spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other components (Fig. 3-11B). As the scar matures, there is progressive vascular regression, which eventually transforms the granulation tissue into a pale, largely avascular scar.

## Growth Factors Involved in ECM Deposition and Scar Formation

Many growth factors are involved in these processes, including TGF- $\beta$ , PDGF, and FGF. Because FGF was described earlier. Here we briefly describe some properties of TGF- $\beta$  and PDGF.

TGF- $\beta$  belongs to a family of homologous polypeptides (TGF- $\beta$ 1, - $\beta$ 2, and - $\beta$ 3) that includes other proteins, activins, and inhibins. TGF- $\beta$ 1 has a widespread distribution and is usually referred to as TGF- $\beta$ . It binds to cell surface receptors with serine/threonine kinase activity, triggering the phosphorylation of transcription factors, which then mediate many and often opposite effects, depending on the cell type and the metabolic state of the tissue. TGF- $\beta$  has two main functions:

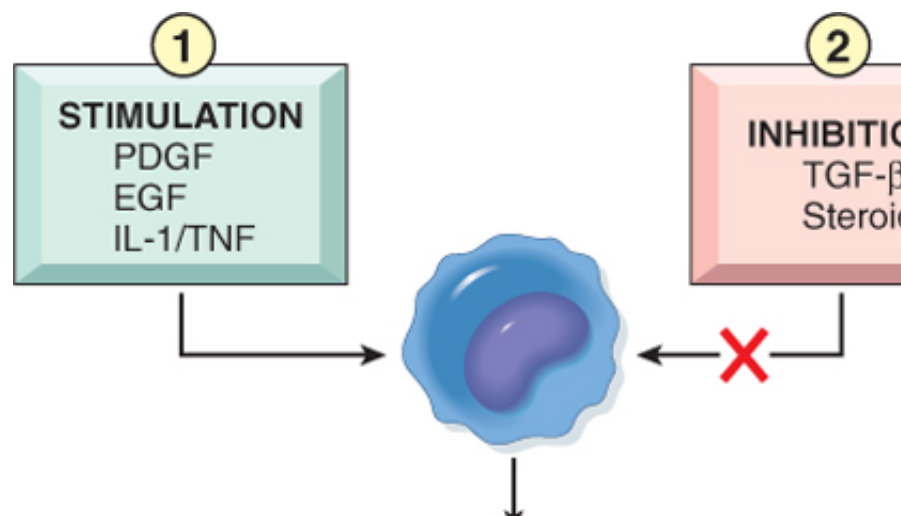
*TGF- $\beta$  is a potent fibrogenic agent.* It stimulates the production of collagen, fibronectin, and proteoglycans, and inhibits degradation by both decreasing proteinase activity and increasing the activity of tissue inhibitors of metalloproteinases (discussed below). TGF- $\beta$  is involved not only in scar formation after injury but also in the progression of chronic diseases such as kidney disease that follows chronic inflammation. *TGF- $\beta$  inhibits lymphocyte proliferation and can induce apoptosis.* Mice lacking TGF- $\beta$  have widespread inflammation and abundant lymphocyte proliferation.

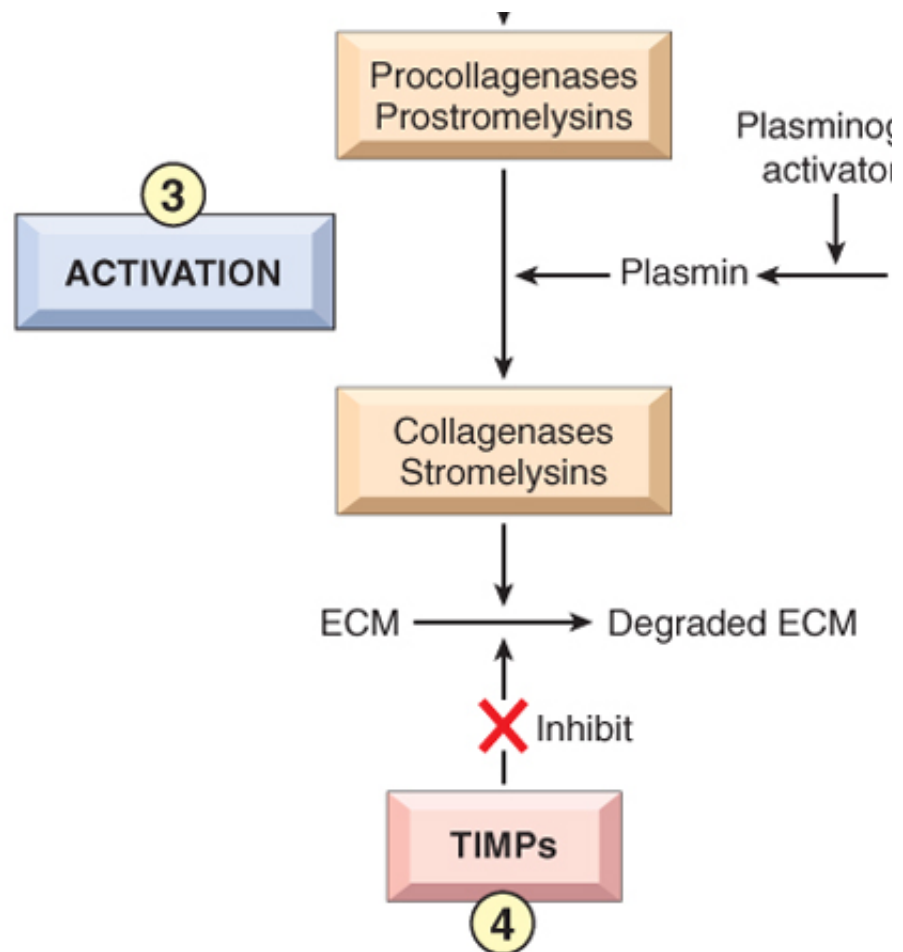
PDGF belongs to a family of closely related proteins, each consisting of two chains, designated A and B, with four isoforms, designated AA, AB, BB, CC, and DD. PDGFs bind to receptors designated as PDGFR  $\alpha$  and  $\beta$ . The  $\alpha$  isoform is the prototype for the family and is referred to as PDGF. It is stored in platelets and released on platelet activation. PDGF causes migratory and proliferative responses in fibroblasts, smooth muscle cells, and macrophages.

Cytokines (discussed in Chapter 2 as mediators of inflammation and in Chapter 5, in the context of growth factors) participate in ECM deposition and scar formation. IL-1 and TNF, for example, have a fibrogenic effect. They are also chemotactic for fibroblasts and stimulate the synthesis of collagen.

### ECM and Tissue Remodeling

The transition from granulation tissue to scar involves shifts in the composition of the ECM; even after the initial repair, the ECM continues to be modified and remodeled. *The outcome of the repair process is, in part, a balance between synthesis and degradation.* We have already discussed the cells and factors that regulate ECM synthesis. The degradation of ECM components is accomplished by a family of matrix metalloproteinases (MMPs), which are dependent on zinc. MMPs should be distinguished from neutrophil elastase, cathepsin G, plasmin, and other *serine proteinases*, which are not metalloenzymes. MMPs include *interstitial collagenases*, which cleave fibrillar collagen (MMP-1, -2, and -13); *stromelysins* (MMP-3, -10, and -11), which degrade amorphous collagen and fibronectin; and *matrilysins* (MMP-7, -9, and -12), which degrade proteoglycans, laminin, fibronectin, and amorphous collagen.





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 Figure 3-13 Matrix metalloproteinase regulation. The four mechanisms shown include (1) regulation of synthesis inhibition of synthesis by corticosteroids or transforming growth factor  $\beta$  (TGF- $\beta$ ), (3) regulation of the activation blockade of the enzymes by specific tissue inhibitors of metalloproteinases (TIMPs). ECM, Extracellular matrix; E PDGF, platelet-derived growth factor; TNF, tumor necrosis factor. (Modified from Matrisian LM: Metalloproteinases Genet 6:122, 1990.)

MMPs are produced by a variety of cell types (fibroblasts, macrophages, neutrophils, synovial cell synthesis and secretion are regulated by growth factors, cytokines, and other agents (Fig. 3-13). They may be suppressed pharmacologically with steroids. Given the potential to wreak havoc in tissues *controlled*. Thus, they are typically elaborated as inactive (*zymogen*) precursors that must be first chemicals or proteases (e.g., plasmin) likely to be present only at sites of injury. In addition, active by specific tissue inhibitors of metalloproteinases (*TIMPs*), produced by most mesenchymal cells. and temporally regulated in healing wounds. They are essential in the debridement of injured sites

A large and important family of enzymes related to MMPs is called *ADAM* (a disintegrin and metal the plasma membrane and cleave and release extracellular domains of cell surface proteins, such the EGF family.

### SUMMARY

**Regeneration and Repair by Connective Tissue** Tissues can be repaired complete restoration of form and function, or by replacement with connectiv formation The main components of connective tissue repair are angiogenesis proliferation of fibroblasts, collagen synthesis, and connective tissue remodel tissue starts with the formation of granulation tissue and culminates in the la



tissue. Multiple growth factors stimulate the proliferation of the cell types involved in tissue repair. TGF- $\beta$  is a potent fibrogenic agent; ECM deposition depends on the balance between fibroblast production of ECM and metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs.



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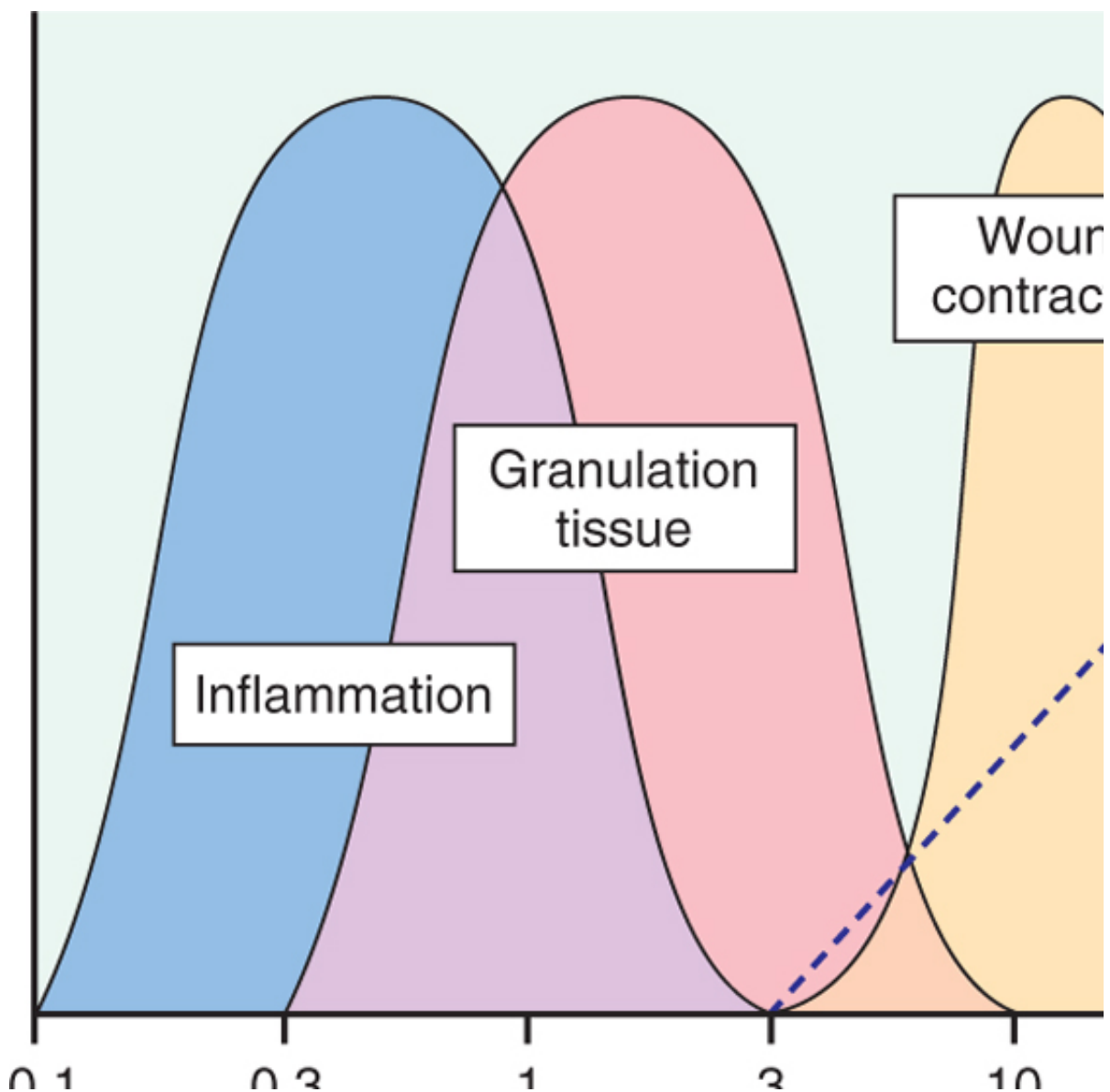


## CUTANEOUS WOUND HEALING

**Table 3-2. Growth Factors and Cytokines Affecting Various Steps in Wound H**

Epithelial proliferation	EGF, TGF- $\alpha$ , KGF, HGF
Monocyte chemotaxis	PDGF, FGF, TGF- $\beta$
Fibroblast migration	PDGF, FGF, TGF- $\beta$
Fibroblast proliferation	PDGF, EGF, FGF, TNF
Angiogenesis	VEGF, Ang, FGF
Collagen synthesis	TGF- $\beta$ , PDGF
Collagenase <sub>R</sub> secretion	PDGF, FGF, EGF, TNF; TGF- $\beta$ inhibits

Ang, Angiopoietin; TNF, tumor necrosis factor. See Table 3-1 for other abbreviations.



Days

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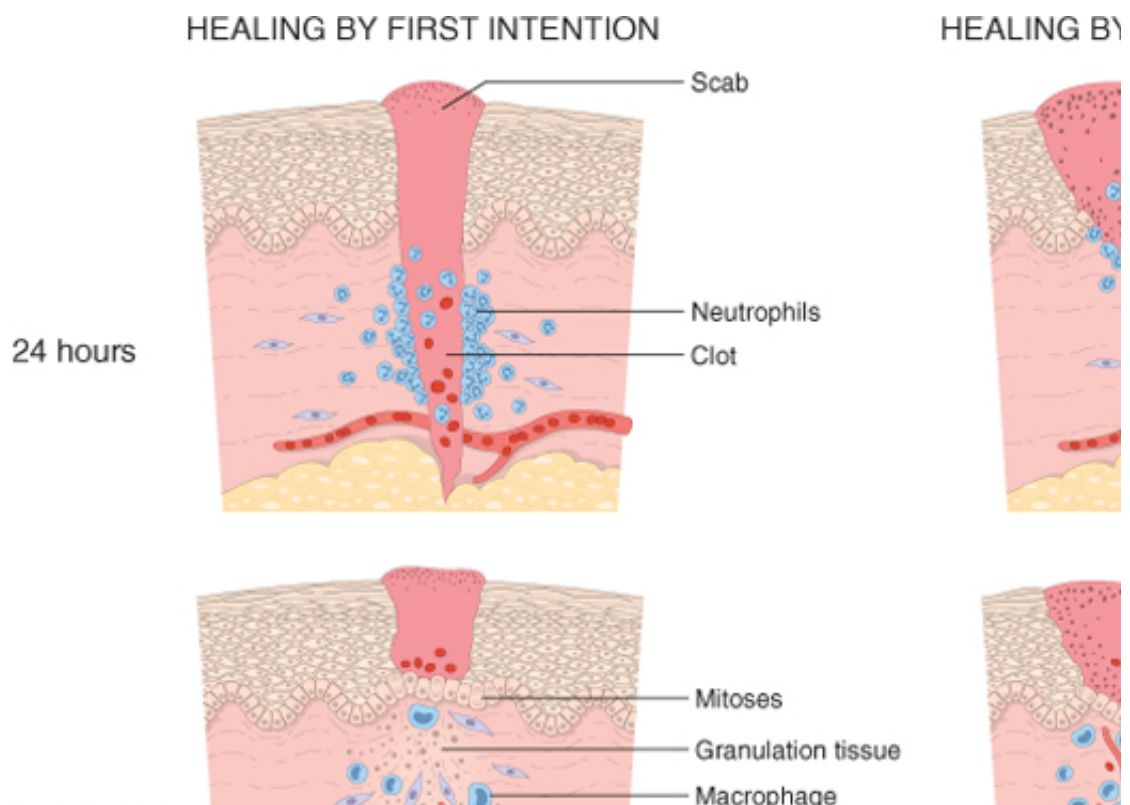
Figure 3-14 Phases of wound healing. Wound contraction occurs only in healing by second intention (see text). (D Basic biologic considerations. J Am Acad Dermatol 13:702, 1985.)

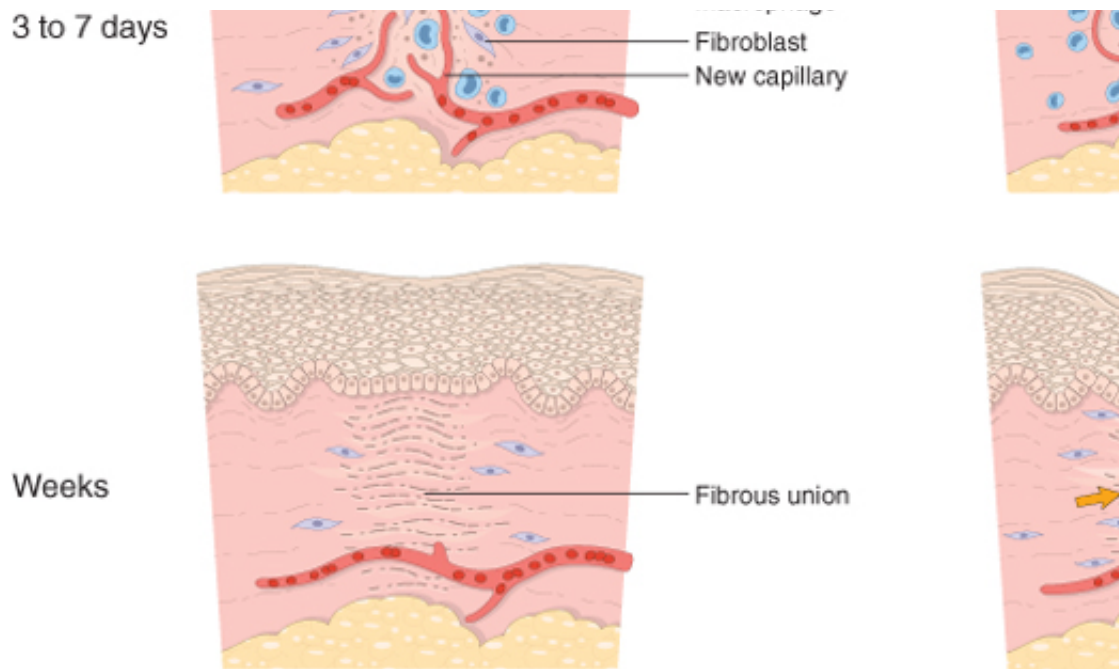
So far, we have discussed general aspects of healing. In this section we specifically describe the *healing*). This is a process that involves both epithelial regeneration and the formation of connective tissue. The general principles that apply to wound healing in all tissues. Specialized cell types first clear the wound of debris and bacteria. Then, fibroblasts migrate into the wound and build the scaffolding to fill in any defect. Re-epithelialization of the wound surface takes place most rapidly in healing by first intention. The events are orchestrated by interplay of growth factors and ECM; physical conditions, changes in cell shape, also contribute. The properties of various growth factors involved in repair are listed in Table 3-1. The main factors that act at each wound healing step. However, one should be aware that different tissues and features that modify the basic scheme discussed here.

Cutaneous wound healing has three main phases: (1) *inflammation*, (2) *formation of granulation tissue*, and (3) *remodeling* (Fig. 3-14). Larger wounds also *contract* during the healing process (discussed later). The three phases of wound healing overlap to a great extent and cannot be completely separated from each other. Basically, *healing of cutaneous wounds can occur by first or second intention*.

### Healing by First Intention

One of the simplest examples of wound repair is the healing of a clean, uninfected surgical incision (Fig. 3-15). This is referred to as *primary union*, or *healing by first intention*. The incision causes only focal disruption of membrane continuity and death of a relatively few epithelial and connective tissue cells. As a result, there is minimal wound contraction. The narrow incision is rapidly invaded by granulation tissue and covered by new epithelium.





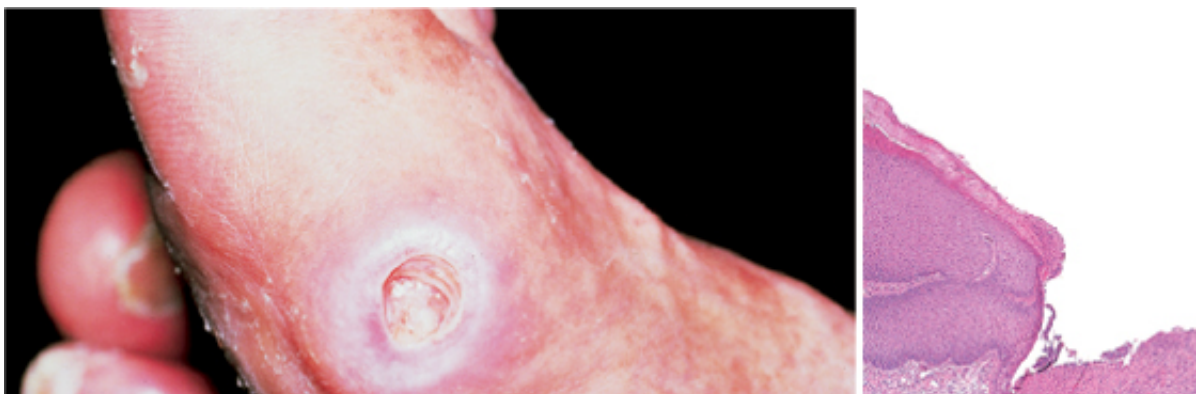
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Figure 3-15 Steps in wound healing by first intention (*left*) and second intention (*right*). In the latter, note the la contraction.

*Within 24 hours*, neutrophils are seen at the incision margin, migrating toward the *fibrin clot*. Basa begin to show increased mitotic activity. Within 24 to 48 hours, epithelial cells from both edges ha the dermis, depositing basement membrane components as they progress. The cells meet in the yielding a thin but continuous epithelial layer.

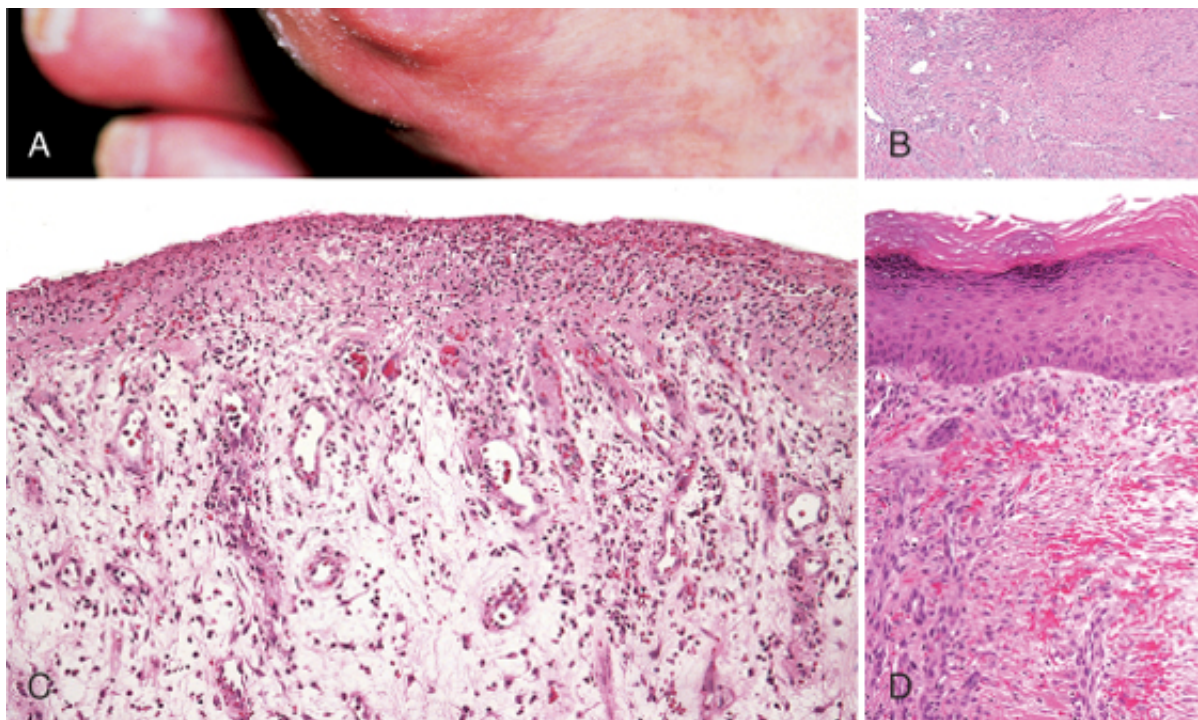
*By day 3*, neutrophils have been largely replaced by macrophages, and granulation tissue progres Collagen fibers are now evident at the incision margins, but these are vertically oriented and do n proliferation continues, yielding a thickened epidermal covering layer.

*By day 5*, neovascularization reaches its peak as granulation tissue fills the incisional space. Colla begin to bridge the incision. The epidermis recovers its normal thickness as differentiation of surfa architecture with surface keratinization.

*During the second week*, there is continued collagen accumulation and fibroblast proliferation. The increased vascularity are substantially diminished. The long process of "blanching" begins, accom within the incisional scar and the regression of vascular channels.







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Figure 3-16 Healing of skin ulcers. **A**, Pressure ulcer of the skin, commonly found in diabetic patients. **B**, A skin ulceration. **C**, A thin layer of epidermal re-epithelialization, and extensive granulation tissue formation in the dermis. **D**, Wound contraction and granulation tissue. (Courtesy of Z. Argenyi, MD, University of Washington)

By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammation. The overlying epidermis is essentially normal. However, the dermal appendages destroyed in the line of the incision do not regenerate. The tensile strength of the wound increases with time, as described later.

### Healing by Second Intention

When cell or tissue loss is more extensive, such as in large wounds, abscess formation, and ulceration, as is also the case after infarction in parenchymal organs. In second-intention healing, a wound heals by contraction and granulation tissue formation (Figs. 3-15 and 3-16), the inflammatory reaction is more intense, there is abundant development of granulation tissue, and the wound contracts by the action of *myofibroblasts*. This is followed by accumulation of ECM and formation of a scar.

Secondary healing differs from primary healing in several respects:

*A larger clot or scab* rich in fibrin and fibronectin forms at the surface of the wound. *Inflammation* is more intense. *Granulation tissue* defects have a greater volume of necrotic debris, exudate, and fibrin that must be reabsorbed. *Wound contraction* is more extensive. *Scar formation* is more pronounced. *Healing time* is longer. *Healing by second intention* has a greater potential for secondary, inflammation-mediated, injury (Chapter 2). *Much larger areas of tissue loss* require a greater volume of granulation tissue to fill in the gaps and provide a scaffold for the regrowth of tissue epithelium. A greater volume of granulation tissue generally results in a larger scar. *Healing involves wound contraction*. Within 6 weeks, for example, large skin defects may be closed by contraction. This process has been ascribed to the presence of *myofibroblasts* exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells.

### Wound Strength

Carefully sutured wounds have approximately 70% of the strength of unwounded skin, largely because of the presence of sutures. When sutures are removed, usually at 1 week, wound strength is approximately 10% of that of unwounded skin. Over the next 4 weeks, the recovery of tensile strength results from collagen synthesis exceeding degradation and from structural modifications of collagen (e.g., cross-linking and increased fiber size) when exposed to ultraviolet light.

and from structural modifications of collagen (e.g., cross-linking and increased fiber size) when sy strength reaches approximately 70% to 80% of normal by 3 months but usually does not substant



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## PATHOLOGIC ASPECTS OF REPAIR

Wound healing may be altered by a variety of influences, frequently reducing the quality or adequacy of repair. *Important factors are infections and diabetes.* Variables that modify wound healing may be extrinsic (e.g.,

*Infection* is the single most important cause of delay in healing; it prolongs the inflammatory response and increases the local tissue injury. *Nutrition* has profound effects on wound healing; protein deficiency and vitamin C deficiency, inhibits collagen synthesis and retards healing. *Glucocorticoids* (steroids) have both pro-inflammatory and anti-inflammatory effects, and their administration may result in poor wound strength due to diminished collagen synthesis; however, the anti-inflammatory effects of glucocorticoids are desirable. For example, in corticosteroid therapy, they are sometimes prescribed (along with antibiotics) to reduce the likelihood of opacity that may result from infection. *Mechanical variables* such as increased local pressure or torsion may cause wounds to pull apart or to heal with distortion. *Foreign bodies* such as fragments of steel, glass, or even bone impede healing. *The type (and volume) of injury* also affects healing. *Restoration can occur only in tissues composed of stable and labile cells*; even then, extensive injury results in incomplete tissue regeneration and at least partial loss of function. *Injury to tissues composed of stable cells* results in scarring with, at most, attempts at functional compensation by the remaining viable cells. *The location of the injury* and the character of the tissue in which the injury occurs also affect healing. For example, *inflammation arising in tissue spaces (e.g., pleural, peritoneal, synovial cavities)* is usually resolved by absorption of the exudate. Subsequent repair may occur by digestion of the exudate, initiated by the proteolytic enzymes in the exudate. This is called *resolution*, and in the absence of cellular necrosis, normal tissue is restored. However, in the setting of larger accumulations, the exudate undergoes *organization*: granulation tissue forms, and a fibrous scar ultimately forms.



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Figure 3-17 Keloid. **A**, Excess collagen deposition in the skin forming a raised scar known as a keloid. **B**, Thick collagen bundles and fibroblasts in keloid tissue. (Reprinted from Murphy GF, Herzberg AJ: Atlas of Dermatology. Philadelphia, WB Saunders, 1996. **B**, Courtesy of Z. Argon)

*Aberrations of cell growth and ECM production may occur even in what begins as normal wound healing.* Exuberant amounts of collagen can give rise to prominent, raised scars known as *keloids* (Fig. 3-17). There is a genetic predisposition to keloid formation, and the condition is more common in blacks. Healing wounds on the face or chest may produce tissue that protrudes above the level of the surrounding skin and hinders re-epithelialization. This

*flesh*, and restoration of epithelial continuity requires cautery or surgical resection of the granulation

The mechanisms underlying the disabling *fibrosis* associated with chronic inflammatory diseases, fibrosis, and cirrhosis have many similarities to those involved in normal wound healing. In these conditions, fibrogenesis results from chronic immune reactions that sustain the synthesis and secretion of growth factors and proteases. For example, collagen degradation by collagenases, normally important in wound remodeling, is also important in joint destruction seen in rheumatoid arthritis (Chapter 5).

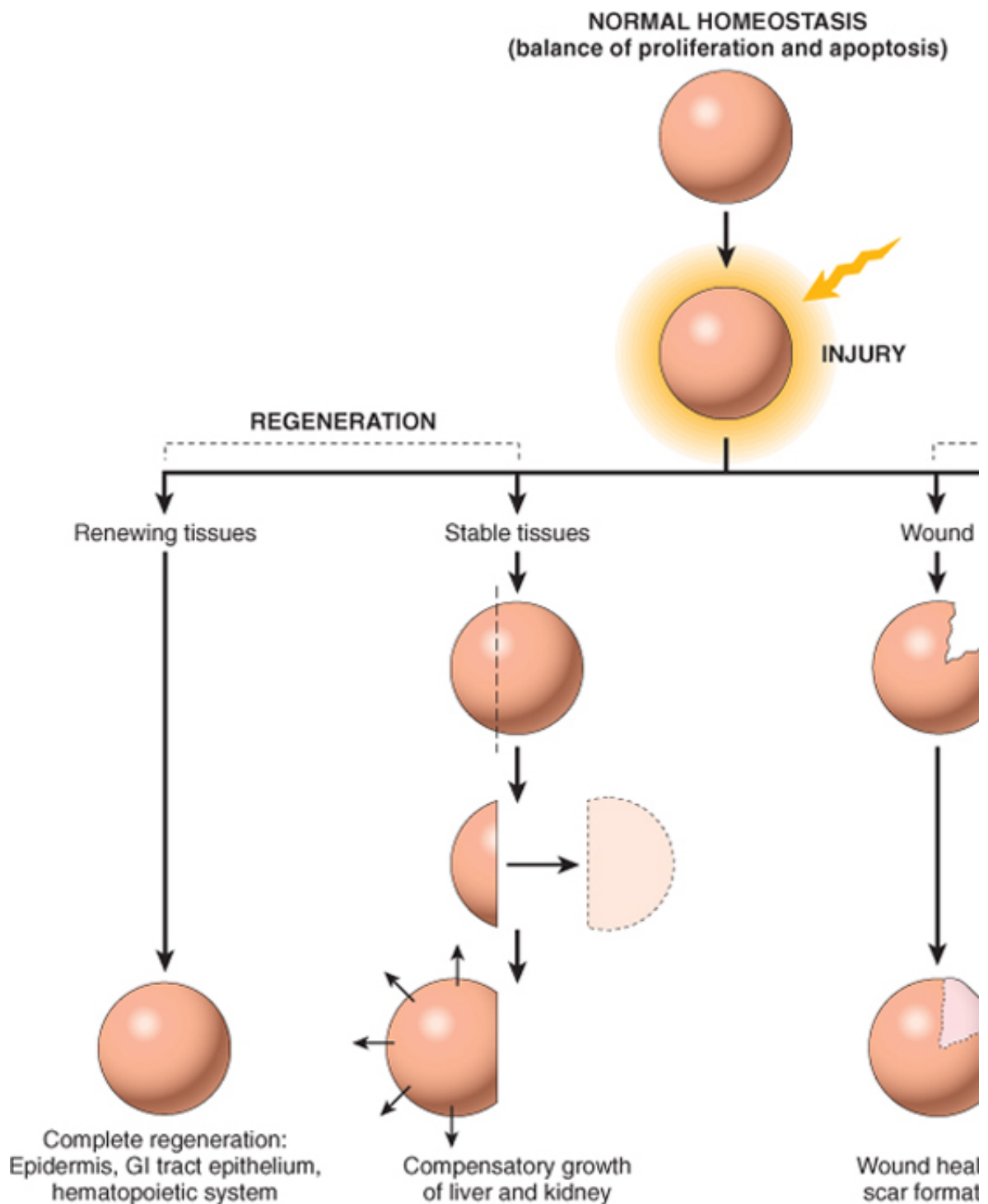




Figure 3-18 Overview of repair responses. Repair after injury can occur by regeneration of cells or tissues that restore the original tissue. If the repair is by fibrosis, it leads to the formation of a scar. Chronic inflammation may cause massive

## SUMMARY

**Cutaneous Wound Healing and Pathologic Aspects of Repair** The main wound healing are inflammation, formation of granulation tissue, and ECM repair. Wounds can heal by primary union (first intention) or secondary union (secondary healing involves more extensive scarring and wound contraction). Wound healing is altered by many conditions, particularly infection and diabetes; the type, volume, and location of injury are important factors for healing. Excessive production of ECM can cause keloid. Persistent stimulation of collagen synthesis in chronic inflammatory disease leads to the formation of a scar.



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## OVERVIEW OF REPAIR PROCESSES

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In this chapter we discussed various processes of tissue repair and their molecular mechanisms. A general overview of these processes is presented in [Figure 3-18](#). We have seen that not all injuries result in permanent damage, and that stable tissues such as the liver and tubular epithelium of the kidney can grow to compensate for tissue loss. Thus, some injuries can be resolved with almost perfect restoration of structure and function by cell and tissue regeneration. More often, though—depending on the type and extent of injury, the nature of the injured tissue, and persistence of inflammatory stimuli—injury results in some degree of residual scarring. Although it is functionally imperfect, a scar provides a resilient permanent patch that allows the remaining intact parenchyma to continue functioning. Occasionally, however, the scarring may be so large that it results in massive fibrosis, or so situated that it causes permanent dysfunction. In a healed myocardial infarct, for example, the fibrous tissue not only represents a loss of functioning muscle but by involving the conduction system may cause heart blocks or provide a surface for thrombus formation.

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## 4 Hemodynamic Disorders, Thrombosis, and Shock

The health of cells and tissues depends not only on an *intact circulation* to deliver oxygen and remove wastes but also on *normal fluid homeostasis*. Normal fluid homeostasis requires vessel wall integrity as well as maintenance of intravascular pressure and osmolarity within certain physiologic ranges. Increases in vascular volume or pressure, decreases in plasma protein content, or alterations in endothelial function can result in a net outward movement of water across the vascular wall. Such water extravasation into interstitial spaces is called *edema*; depending on its location, edema may have minimal or profound effects. Thus, in the lower extremities edema fluid causes primarily swelling; however, in the lungs, edema fluid will fill alveoli and can result in life-threatening breathing difficulties.

Normal fluid homeostasis also means maintaining blood as a liquid until such time as injury necessitates formation of a clot. Absence of clotting after vascular injury results in *hemorrhage*; local bleeding can compromise regional tissue perfusion, while more extensive hemorrhage can result in hypotension (*shock*) and death. Conversely, inappropriate clotting (*thrombosis*) or migration of clots (*embolism*) can obstruct tissue blood supplies and cause cell death (*infarction*).

Abnormal fluid homeostasis (i.e., hemorrhage or thrombosis) underlies three of the most important causes of morbidity and mortality in Western society: myocardial infarction, pulmonary embolism, and cerebrovascular accident (stroke).







## EDEMA

Approximately 60% of lean body weight is water, two-thirds of which is intracellular and the remainder mostly as interstitial fluid; only 5% of total body water is in blood plasma. The term *edema* signifies spaces; fluid collections in different body cavities are variously designated *hydrothorax*, *hydropericardium* (more commonly called *ascites*). *Anasarca* is a severe and generalized edema with profound subcutaneous edema.

There are several pathophysiologic categories of edema ([Table 4-1](#)). The mechanism of inflammatory edema is discussed in [Chapter 2](#); *noninflammatory causes of edema* are described in [Chapter 3](#).

**Table 4-1. Pathophysiologic Categories of Edema**

<b>Increased Hydrostatic Pressure</b>
Impaired venous return
Congestive heart failure
Constrictive pericarditis
Ascites (liver cirrhosis)
Venous obstruction or compression
Thrombosis
External pressure (e.g., mass)
Lower extremity inactivity with prolonged dependency
Arteriolar dilation
Heat
Neurohumoral dysregulation
<b>Reduced Plasma Osmotic Pressure (Hypoproteinemia)</b>
Protein-losing glomerulopathies (nephrotic syndrome)
Liver cirrhosis (ascites)
Malnutrition
Protein-losing gastroenteropathy
<b>Lymphatic Obstruction</b>
Inflammatory
Neoplastic
Postsurgical
Postirradiation
<b>Sodium Retention</b>
Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-aldosterone secretion
<b>Inflammation</b>
Acute inflammation
Chronic inflammation
Angiogenesis

Modified from Leaf A, Cotran RS: Renal Pathophysiology, 3rd ed. New York, Oxford University Press, 1985, p 146.

The movement of fluid between vascular and interstitial spaces is controlled mainly by the opposing forces of hydrostatic and oncotic pressures.

pressure and plasma colloid osmotic pressure. Normally, the exit of fluid into the interstitium from is nearly balanced by inflow at the venular end; the lymphatics drain a small residual amount of ex capillary pressure or diminished colloid osmotic pressure can result in increased interstitial fluid (F accumulates in either case, the increased tissue hydrostatic and plasma osmotic pressures event water re-enters the venules. Excess interstitial edema fluid is removed by lymphatic drainage, ultil the thoracic duct (see Fig. 4-1); clearly, lymphatic obstruction (e.g., due to scarring or tumor) can i edema. Finally, sodium retention (with its obligatory associated water) due to renal disease can al

The edema fluid occurring with volume or pressure overload, or under conditions of reduced plas *transudate*; it has a specific gravity less than 1.012. Conversely, because of the increased vascul protein-rich *exudate* with a specific gravity that is usually greater than 1.020 (see Fig. 2-3, Chapte

#### Increased Hydrostatic Pressure

*Localized* increases in intravascular pressure can result from impaired venous return; for example thrombosis can cause edema restricted to the distal portion of the affected leg. *Generalized* incre systemic edema, occur most commonly in *congestive heart failure* (Chapter 11), affecting right ve increased venous hydrostatic pressure is contributory, the pathogenesis of cardiac edema is more failure, reduced cardiac output translates into reduced renal perfusion. Renal hypoperfusion in tur aldosterone axis, inducing sodium and water retention by the kidneys (*secondary aldosteronism*). increase intravascular volume and thereby improve cardiac output to restore normal renal perfusio increase cardiac output, the extra fluid load causes increased venous pressure and, eventually, ei or renal water retention reduced (e.g., by salt restriction, diuretics, or aldosterone antagonists), a worsening edema ensues. Although salt restriction, diuretics, and aldosterone antagonists are dis congestive heart failure, it should be understood that they are also of value in the management of variety of other causes.

#### Reduced Plasma Osmotic Pressure

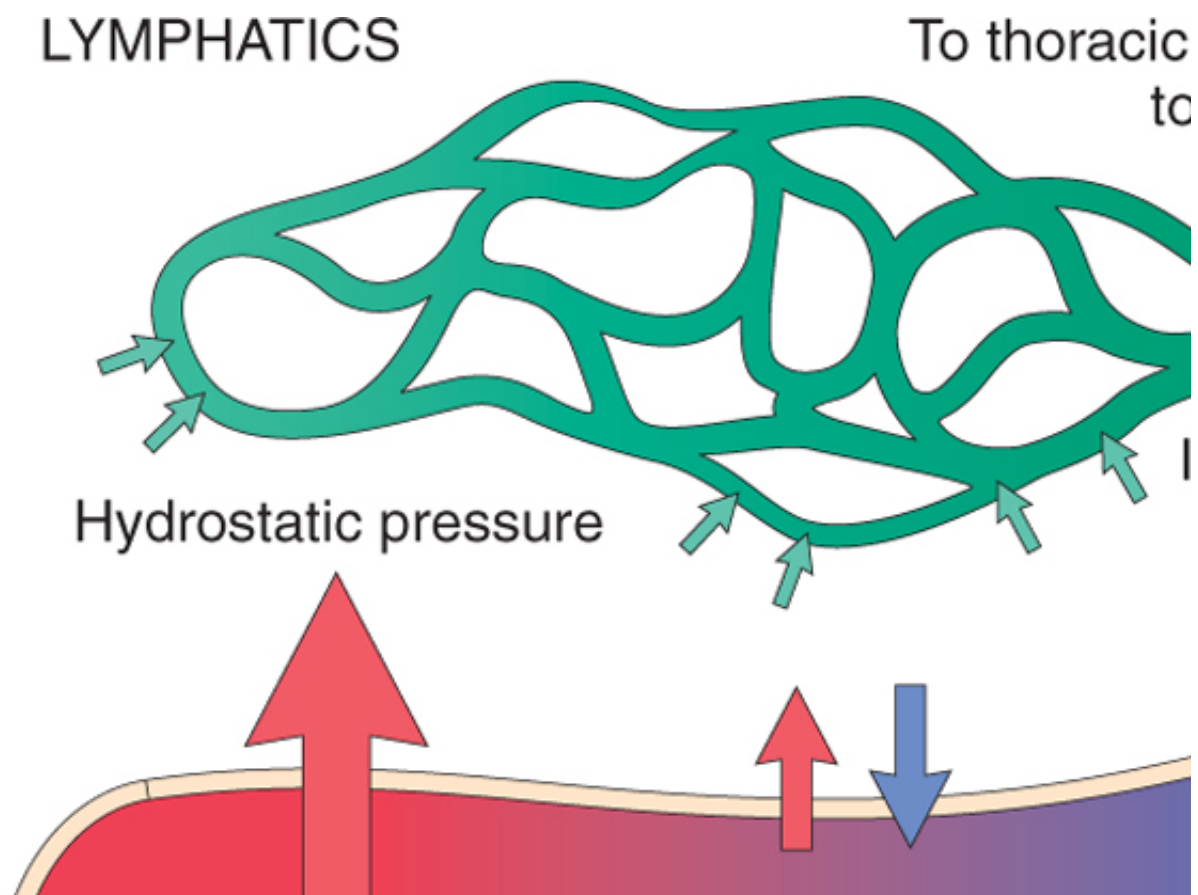
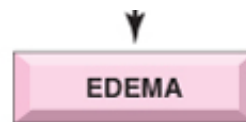




Figure 4-1 Variables affecting fluid transit across capillary walls. Capillary hydrostatic and osmotic forces are normal fluid across the capillary bed. However, *increased* hydrostatic pressure or *diminished* plasma osmotic pressure lead to edema. As the interstitial fluid pressure increases, tissue lymphatics remove much of the excess volume, eventually returning it to the venous system. If the ability of the lymphatics to drain tissue fluid is exceeded, persistent tissue edema results.



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Figure 4-2 Pathways leading to systemic edema due to primary heart failure, primary renal failure, or reduced plasma protein synthesis (e.g., diminished hepatic synthesis, or protein loss due to the nephrotic syndrome). ADH, antidiuretic hormone.

Albumin is the serum protein most responsible for maintaining intravascular colloid osmotic pressure. When albumin is inadequately synthesized or is lost from the circulation. An important cause of all (Chapter 14), in which glomerular capillary walls become leaky; patients typically present with generalized edema. Protein synthesis occurs in the setting of diffuse liver diseases (e.g., cirrhosis; Chapter 16) or due to protein loss. Reduced plasma osmotic pressure leads to a net movement of fluid into the interstitial tissues with Predictably, reduced intravascular volume leads to renal hypoperfusion followed by secondary aldosterone secretion. Salt and water cannot correct the plasma volume deficit since the primary defect of low serum protein failure, edema precipitated by low protein is exacerbated by secondary salt and fluid retention.

#### *Lymphatic Obstruction*

Impaired lymphatic drainage and consequent *lymphedema* is usually localized; it can result from infection, tumor, or radiation. For example, the parasitic infection *filariasis* can cause extensive inguinal lymphatic and lymph node enlargement. External genitalia and lower limbs can be so massive as to earn the appellation *elephantiasis*. Carcinoma resection and/or irradiation of the associated axillary lymph nodes; the resultant scarring and loss of lymphatics cause upper extremity edema. In breast carcinoma infiltration and obstruction of superficial lymphatics cause skin thickening, the so-called *peau d'orange* (orange peel) appearance. Such a finely pitted surface results from retraction of skin at the site of hair follicles.

#### *Sodium and Water Retention*

Salt retention can also be a primary cause of edema. Increased salt-with the obligate accompanying water retention increases hydrostatic pressure (due to expansion of the intravascular volume) and reduced vascular osmotic pressure. Any compromise of renal function, as in *poststreptococcal glomerulonephritis* and *acute renal failure*.

### **SUMMARY**

#### **Edema**

Edema is extravasation of fluid from vessels into interstitial spaces; the fluid may be protein poor (transudate) or may be protein rich (exudate). Edema results from any of the following: Increased hydrostatic pressure, caused by a reduction in venous return (e.g., heart failure) Decreased colloid osmotic pressure, caused by reduced concentration of albumin (due to decreased synthesis, as in liver disease, or increased loss, as in nephrotic disease) Lymphatic obstruction that impairs interstitial fluid clearance (e.g., certain infections) Primary renal sodium retention (in renal failure) Increased vascular permeability (in inflammation)

#### **Morphology**

Edema is most easily recognized grossly; microscopically, edema fluid is reflected by separation of the extracellular matrix elements with subtle cell swelling. Although any body part may be involved, edema is most commonly encountered in subcutaneous tissues.

**Subcutaneous edema** can be diffuse or more prominent in regions with high hydrostatic pressure. Ultimate distribution depends on the underlying etiology. Even diffuse edema is usually more prominent in certain body areas as a result of the effects of gravity; a gravity-dependent distribution is called **dependent edema** (e.g., involving the legs when standing, or involving the sacrum when lying down). **Dependent edema is a prominent feature of cardiac failure, particularly of the right heart.**



due to **renal dysfunction** or **nephrotic syndrome** is generally more severe than in **all parts of the body equally**. Nevertheless, severe edema early in the disease occurs disproportionately in tissues with a loose connective tissue matrix (e.g., the eyelids **edema**). Finger pressure over significantly edematous subcutaneous tissue displaces and leaves a finger-shaped depression, so-called **pitting edema**.

**Pulmonary edema** is a common clinical problem most frequently seen in the setting of heart failure (with a dependent distribution in the lungs), but it also occurs in renal failure, acute respiratory distress syndrome (ARDS; [Chapter 13](#)), pulmonary infections, and hypersensitivity reactions. Edematous lung tissue weighs two to three times their normal weight, and sectioning reveals frothy, sometimes hemorrhagic areas representing a mixture of air, edema fluid, and extravasated red cells.

**Edema of the brain** may be localized to sites of focal injury (e.g., infarct, abscess) or may be generalized, as in encephalitis, hypertensive crises, or obstruction to the brain's venous drainage. Localized edema may result in local or generalized edema, depending on the nature and extent of the injury. In generalized edema, the brain is grossly swollen with narrowed sulci and distended gyri showing the unyielding skull ([Chapter 23](#)).

### *Clinical Correlation*

The effects of edema may range from merely annoying to rapidly fatal. Subcutaneous tissue edema is primarily because it indicates underlying disease; however, when significant it can also impair wound healing. In contrast, pulmonary edema can cause death by interfering with normal ventilatory function. Not only does edema fluid in the alveolar spaces also impede oxygen diffusion, but edema fluid in the interstitial spaces also promotes bacterial infection. Brain edema is serious and can be rapidly fatal. If severe, brain edema can cause herniation through the foramen magnum; the brainstem vascular supply can also be compressed by edema. Either state can injure the medullary centers and can cause death ([Chapter 23](#)).



## HYPEREMIA AND CONGESTION

The terms *hyperemia* and *congestion* both indicate a local increased volume of blood in a particular tissue. Hyperemia is an *active process* resulting from augmented blood flow due to arteriolar dilation (e.g., at sites of inflammation or in skeletal muscle during exercise). The affected tissue is redder than normal because of engorgement with oxygenated blood. Congestion is a *passive process* resulting from impaired venous return out of a tissue. It may occur systemically, as in cardiac failure, or it may be local, resulting from an isolated venous obstruction. The tissue has a blue-red color (*cyanosis*), especially as worsening congestion leads to accumulation of deoxygenated hemoglobin in the affected tissues (Fig. 4-3).

Congestion of capillary beds is closely related to the development of edema, so that congestion and edema commonly occur together. In long-standing congestion, called *chronic passive congestion*, the stasis of poorly oxygenated blood causes chronic hypoxia, which in turn can result in degeneration or death of parenchymal cells and subsequent tissue fibrosis. Capillary rupture at such sites of chronic congestion can also cause small foci of hemorrhage; phagocytosis and catabolism of the erythrocyte debris can result in accumulations of hemosiderin-laden macrophages.

### Morphology

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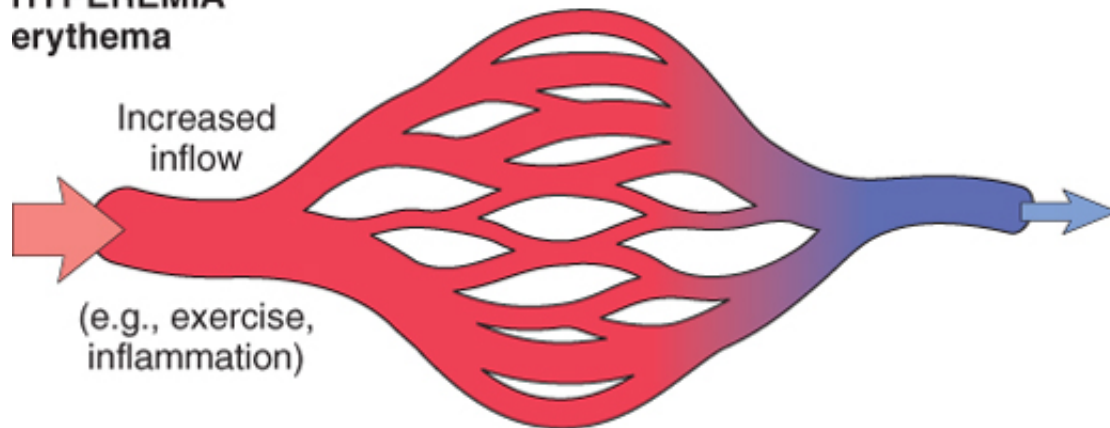
Cut surfaces of hyperemic or congested tissues are hemorrhagic and wet. Microscopically, **acute pulmonary congestion** is characterized by alveolar capillaries engorged with blood; there may also be associated alveolar septal edema and/or focal minute intra-alveolar hemorrhage. In **chronic pulmonary congestion** the septa become thickened and fibrotic, and the alveolar spaces may contain numerous hemosiderin-laden macrophages ("heart failure cells"). In **acute hepatic congestion** the central vein and sinusoids are distended with blood, and there may even be central hepatocyte degeneration; the periportal hepatocytes, better oxygenated because of their proximity to hepatic arterioles, undergo less severe hypoxia and may develop only fatty change. In **chronic passive congestion** of the liver the central regions of the hepatic lobules are grossly red-brown and slightly depressed (because of a loss of cells) and are accentuated against the surrounding zones of uncongested tan, sometimes fatty, liver ("nutmeg liver"; Fig. 4-4A). Microscopically, there is centrilobular necrosis with hepatocyte drop-out, hemorrhage, and hemosiderin-laden macrophages (Fig. 4-4B). In long-standing, severe hepatic congestion (most commonly associated with heart failure), hepatic fibrosis ("cardiac cirrhosis") can develop. It is important to note that because the central portion of the hepatic lobule is the last to receive blood, centrilobular necrosis can also occur whenever there is reduced hepatic blood flow (including shock from any cause); there need not be previous hepatic congestion.

NORMAL

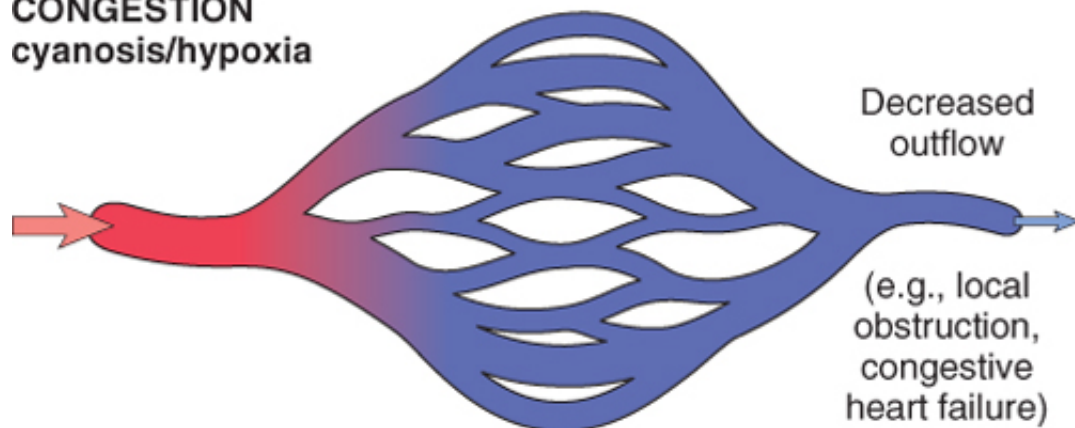




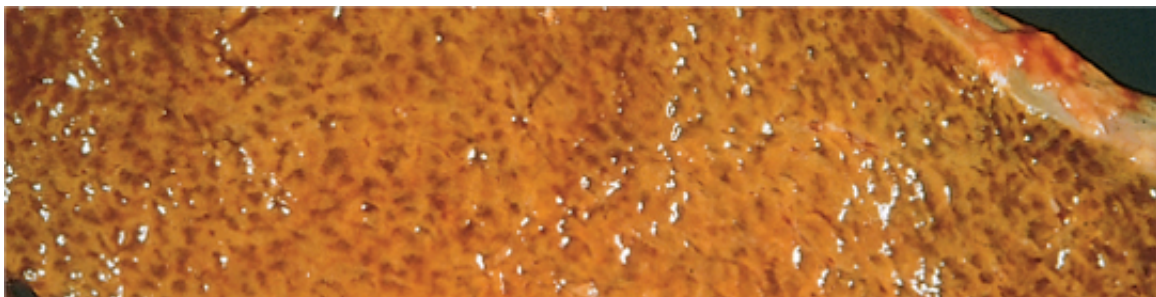
### HYPEREMIA erythema



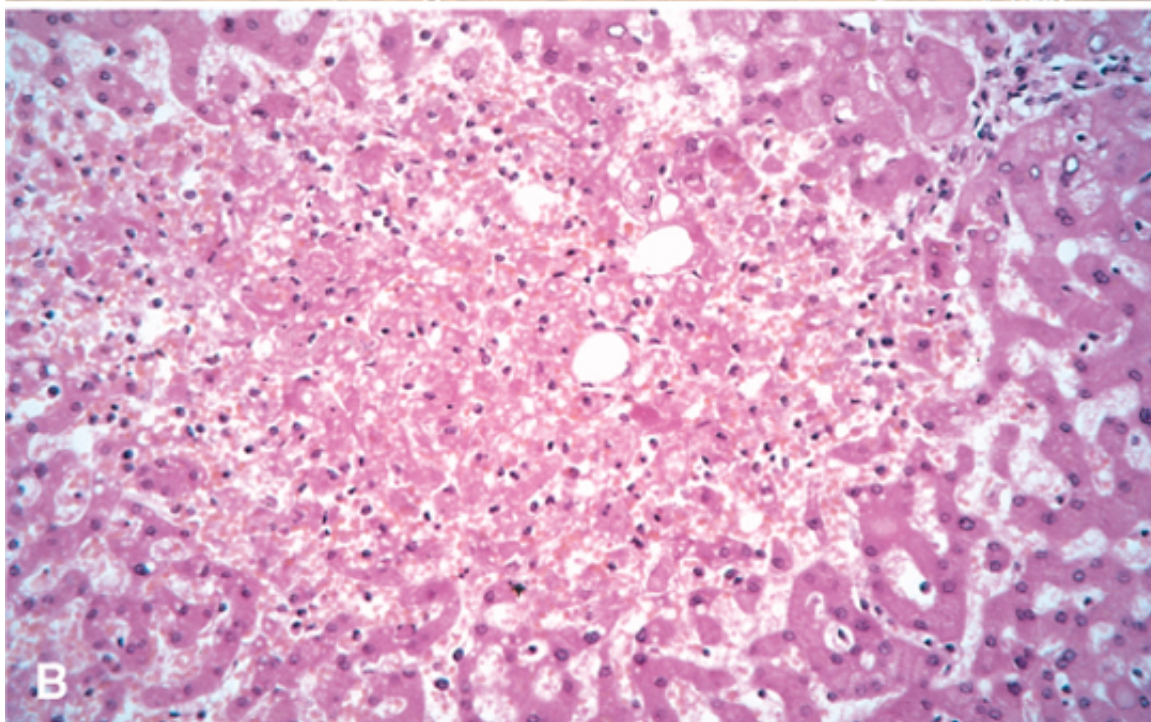
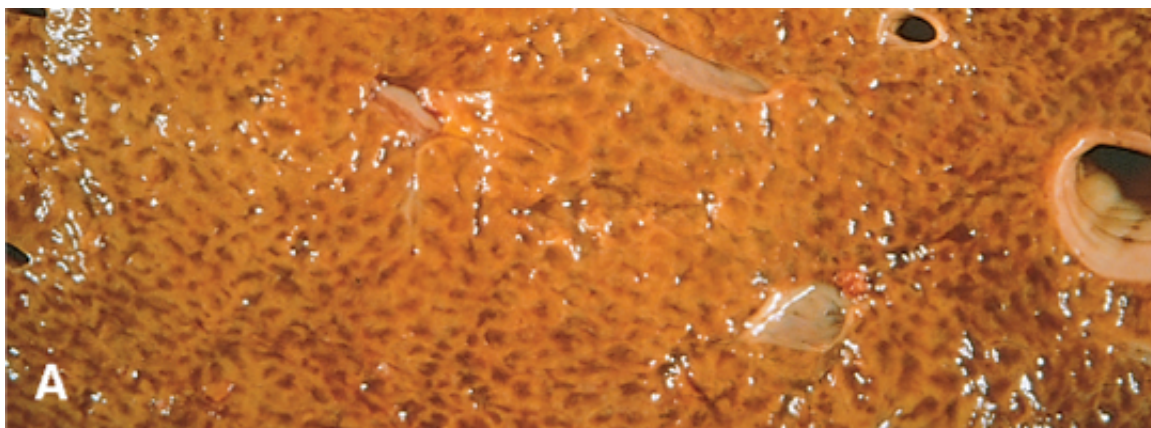
### CONGESTION cyanosis/hypoxia



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 Figure 4-3 Hyperemia versus congestion. In both cases there is an increased volume and pressure of blood in a given tissue with associated capillary dilation and a potential for fluid extravasation. In hyperemia, increased inflow leads to engorgement with oxygenated blood, resulting in *erythema*. In congestion, diminished outflow leads to a capillary bed swollen with deoxygenated venous blood and resulting in *cyanosis*.







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 Figure 4-4 Liver with chronic passive congestion and hemorrhagic necrosis. **A**, Central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, forming a "nutmeg liver" pattern (so called because it resembles the alternating pattern of light and dark seen when a whole nutmeg is cut). **B**, Centrilobular necrosis with degenerating hepatocytes and hemorrhage. (Courtesy of Dr. James Crawford, Department of Pathology, University of Florida, Gainesville, Florida.)



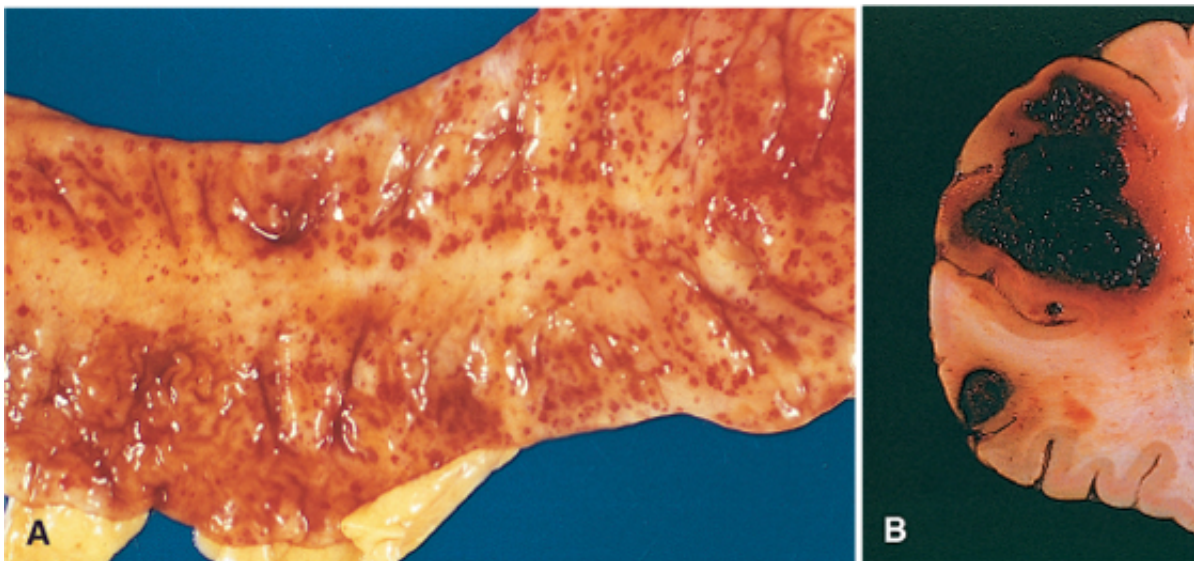


## HEMORRHAGE

Hemorrhage is extravasation of blood from vessels into the extravascular space. As described above, it can occur under conditions of chronic congestion; an increased tendency to hemorrhage (usually with insignificant disorders collectively called *hemorrhagic diatheses*). Rupture of a large artery or vein results in severe hemorrhage due to vascular injury, including trauma, atherosclerosis, or inflammatory or neoplastic erosion of vessel walls.

Hemorrhage can be external or can be confined within a tissue; any accumulation is referred to as a hematoma. It can be relatively insignificant (e.g., a bruise) or can involve so much bleeding as to cause death (e.g., resulting from rupture of a dissecting aortic aneurysm; [Chapter 10](#)). Minute (1- to 2-mm) hemorrhages on mucous membranes, or serosal surfaces are called *petechiae* ([Fig. 4-5A](#)) and are typically associated with increased venous pressure, low platelet counts (*thrombocytopenia*), defective platelet function, or clotting factor deficiencies. Larger (3- to 5-mm) hemorrhages are called *purpura* and can be associated with many of the same disorders. *Purpura* can occur with trauma, vascular inflammation (*vasculitis*), or increased vascular fragility. Localized hemorrhages (hematomas or bruises) are called *ecchymoses*. The erythrocytes in these local hemorrhages are phagocytized by macrophages; the hemoglobin (red-blue color) is enzymatically converted into bilirubin (blue-green) and hemosiderin (golden-brown), accounting for the characteristic color changes in a hematoma over time. Hemorrhages in another of the body cavities are called *hemothorax*, *hemopericardium*, *hemoperitoneum*, or *hemorrhage into body cavities*. Extensive hemorrhages occasionally develop jaundice from the massive breakdown of red blood cells and release of bilirubin.

The clinical significance of hemorrhage depends on the volume and rate of blood loss. Rapid removal of even large volume or slow losses of even larger amounts may have little impact in healthy adults; greater losses can lead to *(hypovolemic) shock* (discussed later). The site of hemorrhage is also important; bleeding that would be inconsequential if located in the brain ([Fig. 4-5B](#)). Finally, chronic or recurrent external blood loss (e.g., from peptic ulcer bleeding) causes a net loss of iron, frequently culminating in an iron deficiency anemia. In contrast to hemorrhage into body cavities or tissues, the iron can be reutilized for hemoglobin synthesis.



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Figure 4-5 **A**, Punctate petechial hemorrhages of the colonic mucosa, a consequence of thrombocytopenia. **B**, Fatal intracerebral hemorrhage, an inconsequential volume of hemorrhage in a critical location, or into a closed space (such as the cranium).



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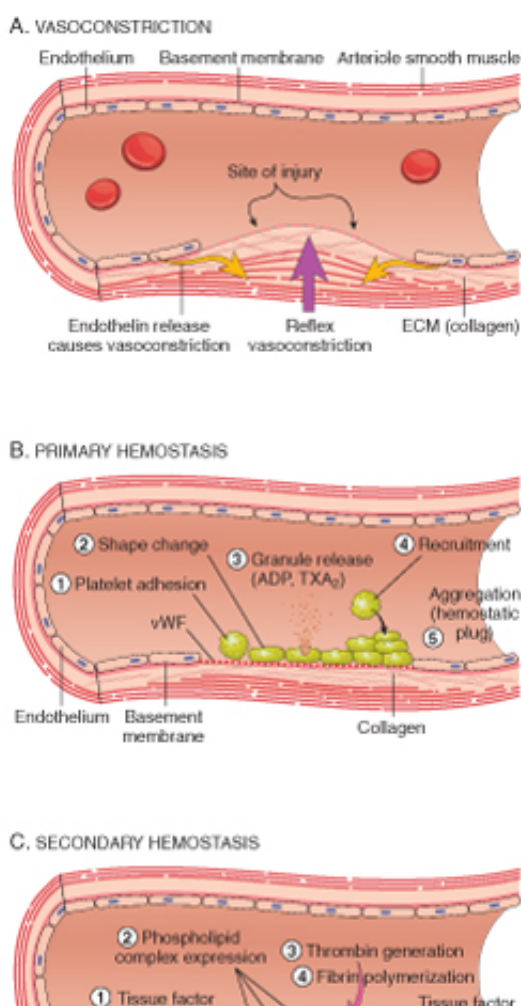
## HEMOSTASIS AND THROMBOSIS

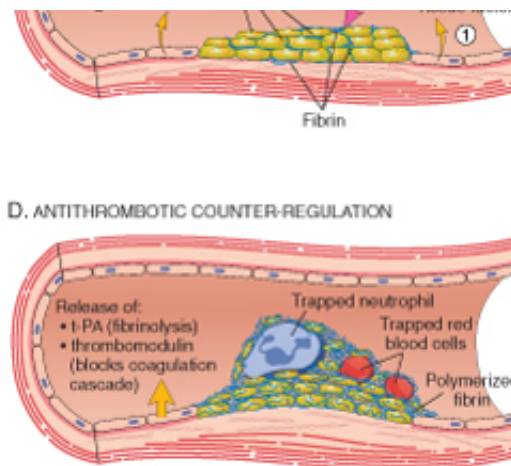
*Normal hemostasis* is a consequence of tightly regulated processes that maintain blood in a fluid, inducing the rapid formation of a localized *hemostatic plug* at the site of vascular injury. The path involves blood clot (*thrombus*) formation in uninjured vessels or thrombotic occlusion of a vessel. Hemostasis and thrombosis involve three components: the *vascular wall*, *platelets*, and the *coagulation* system. This section discusses the process of normal hemostasis and a description of its regulation.

### Normal Hemostasis

The sequence of events in hemostasis at a site of vascular injury is shown in Figure 4-6. After initial *vasoconstriction* occurs mostly as a result of reflex neurogenic mechanisms and is augmented by *endothelin* (a potent endothelium-derived vasoconstrictor; Fig. 4-6A). The effect is transient, and leads to the activation of the platelet and coagulation systems.

*Endothelial injury* also exposes highly thrombogenic subendothelial extracellular matrix, allowing for platelet adhesion. *Activation* of platelets results in a dramatic shape change (from small rounded disks to flat plates) and release of secretory granules. Within minutes the secreted products have recruited additional platelets to the site of injury, forming a *hemostatic plug*; this is the process of *primary hemostasis* (Fig. 4-6B).





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Figure 4-6 Normal hemostasis. **A**, After vascular injury, local neurohumoral factors induce a transient vasoconstriction, exposing the underlying extracellular matrix (ECM) by binding to von Willebrand factor (vWF) and are activated, undergoing a change in shape. **B**, **Adenosine**<sub>2</sub> diphosphate (ADP) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) lead to further platelet aggregation (via binding of fibrinogen to the GPIIb/IIIa receptor), resulting in the formation of the primary hemostatic plug. **C**, Local activation of the coagulation cascade (involving tissue factor and platelet activation) leads to the formation of a definitive secondary hemostatic plug. **D**, Counter-regulatory mechanisms, such as the release of fibrinolytic products (e.g., t-PA) and thrombomodulin (interfering with the coagulation cascade), limit the hemostatic process.

**Tissue factor** is also exposed at the site of injury. Also known as *factor III* and *thromboplastin*, this is a procoagulant glycoprotein synthesized by endothelium. It acts in conjunction with factor VII (see below) to activate the coagulation cascade, eventually culminating in **thrombin**<sub>2</sub> generation. **Thrombin**<sub>2</sub> cleaves **fibrinogen**, creating a fibrin meshwork deposition. **Thrombin**<sub>2</sub> also induces further platelet recruitment and aggregation. The **hemostasis** sequence (Fig. 4-6C) lasts longer than the initial platelet plug.

Polymerized fibrin and platelet aggregates form a solid **permanent plug** to prevent any additional bleeding. Counter-regulatory mechanisms (e.g., *tissue plasminogen activator*, *t-PA*) are set into motion to limit the hemostatic process (Fig. 4-6D).

The following sections discuss these events in greater detail.

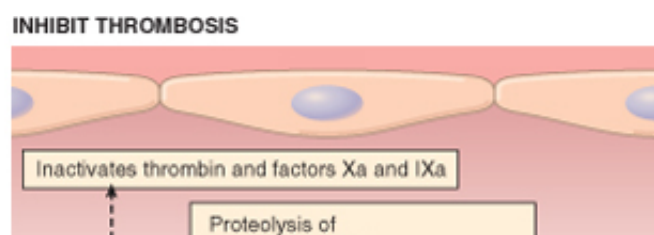
### Endothelium

Endothelial cells modulate several (and frequently opposing) aspects of normal hemostasis. The balance of prothrombotic and antithrombotic activities determines whether thrombus formation, propagation, or dissolution occurs. Endothelial cells have antiplatelet, anticoagulant, and fibrinolytic properties; however, they are capable (after injury or activation) of procoagulant activities (Fig. 4-7). It should also be remembered that endothelium can be activated by plasma mediators, and (most significantly) by cytokines (Chapter 2).

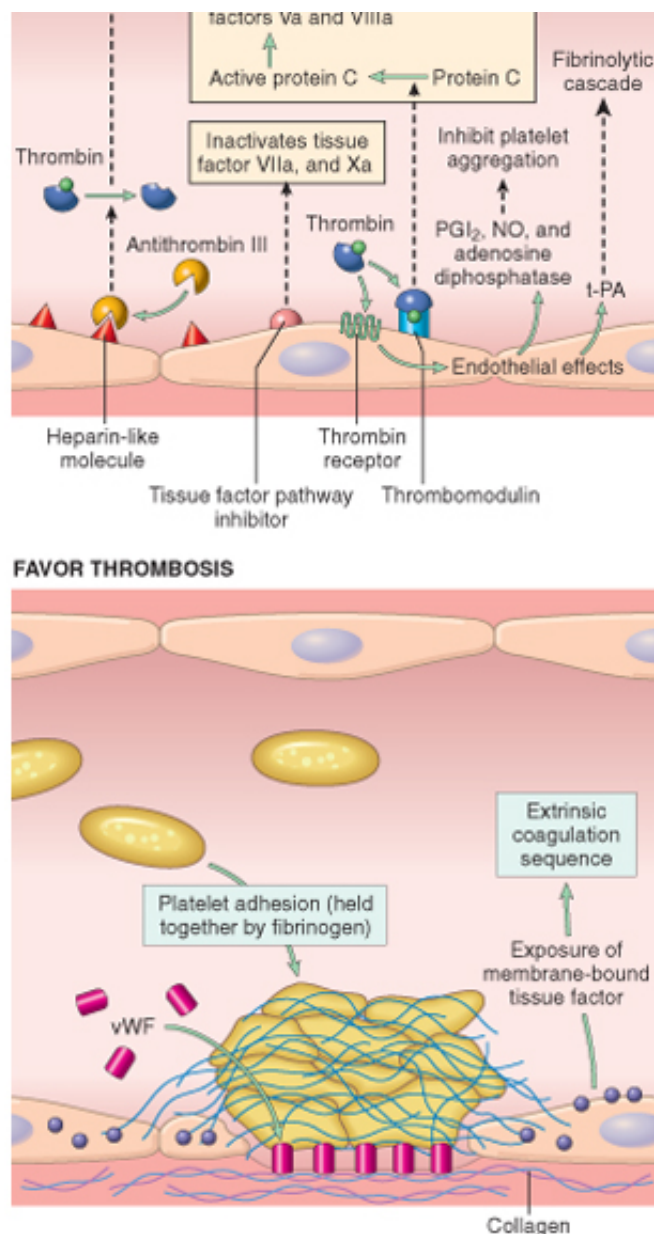
### Antithrombotic Properties

Under most circumstances, endothelial cells maintain an environment that promotes liquid blood flow and prevents aggregation, by inhibiting the coagulation cascade, and by lysing blood clots.

### Antiplatelet Effects







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 Figure 4-7 Pro- and anticoagulant activities of endothelium. Not shown are pro- and antifibrinolytic properties of prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. The  $\text{thrombin}_{\text{R}}$  receptor is also called

An intact endothelium prevents platelets (and plasma coagulation factors) from interacting with the ECM. Nonactivated platelets do not adhere to the endothelium, a property intrinsic to the plasma. If platelets are activated (e.g., after focal endothelial injury), they are inhibited from adhering to the endothelium by prostacyclin (PGI<sub>2</sub>) and nitric oxide<sub>R</sub> (Chapter 2). Both mediators are potent vasodilators. Their synthesis by endothelial cells is stimulated by several factors (e.g.,  $\text{thrombin}_{\text{R}}$  and cytokines). Endothelial cells also elaborate adenosine<sub>R</sub> diphosphatase, which degrades adenosine<sub>R</sub> diphosphate, thereby inhibiting platelet aggregation (see below).

### Anticoagulant Effects

Anticoagulant effects are mediated by membrane-associated, heparin-like molecules and thrombomodulin. These molecules act indirectly; they are cofactors that allow antithrombin III to inactivate  $\text{thrombin}_{\text{R}}$  and other coagulation factors (see later). Thrombomodulin also acts indirectly; it binds to  $\text{thrombin}_{\text{R}}$ , converting it from a

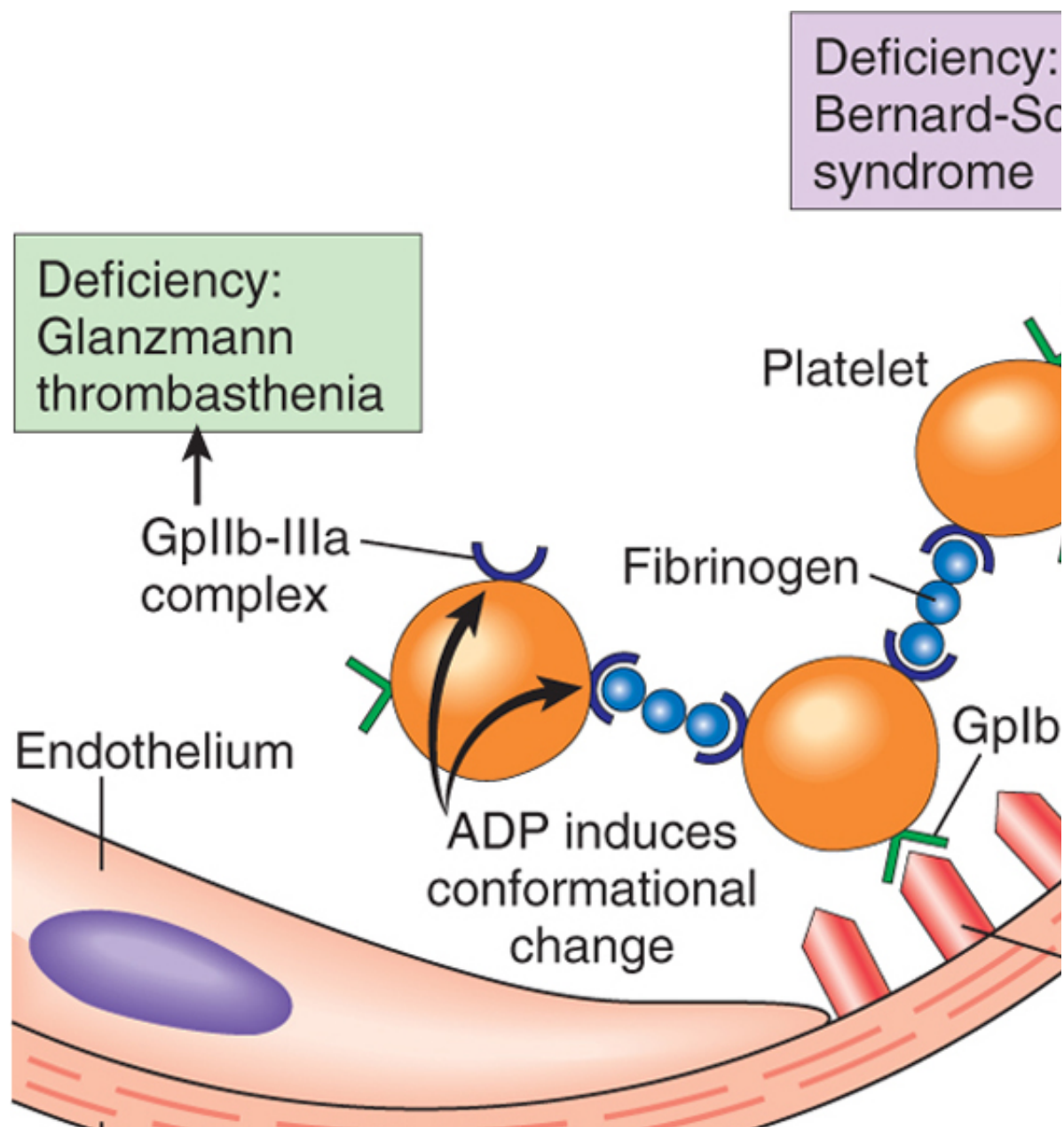
capable of activating the anticoagulant protein C. Activated protein C, in turn, inhibits clotting by p VIIla; it requires protein S, synthesized by endothelial cells, as a cofactor.

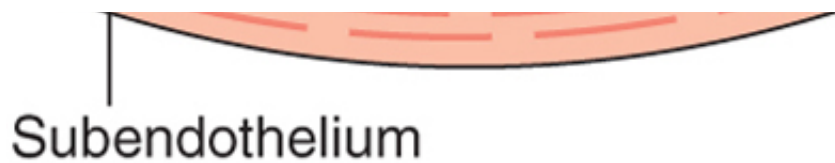
#### ***Fibrinolytic Properties***

Endothelial cells synthesize tissue plasminogen activator (*t-PA*), promoting fibrinolytic activity to c surfaces (see Fig. 4-6D).

#### ***Prothrombotic Properties***

While endothelial cells exhibit properties that usually limit blood clotting, they can also become pro platelets, coagulation proteins, and the fibrinolytic system. Endothelial injury results in platelet adf occurs through *von Willebrand factor (vWF)*, an essential cofactor for binding platelets to collagen circulating and collagen bound) is synthesized largely by normal endothelium. Loss of endotheliur allows circulating vWF to also bind to the basement membrane; in quick order, platelets adhere vi (Fig. 4-8).





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Figure 4-8 Platelet adhesion and aggregation. Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the (GpIb) platelet receptor. Aggregation is accomplished by binding of fibrinogen to platelet GpIIb-IIIa receptors and platelet aggregation. Genetic deficiencies in the various receptors or bridging molecules lead to the diseases indicated in the colored boxes.

Cytokines such as tumor necrosis factor (TNF) or interleukin-1 (IL-1) as well as bacterial endotoxin *tissue factor*; as we will see below, tissue factor activates the extrinsic clotting pathway. By binding to endothelial cells augment the catalytic activities of these coagulation factors. Finally, endothelial cell *inhibitors (PAIs)*, which depress fibrinolysis (not shown in Fig. 4-7).

## SUMMARY

### Contribution of Endothelial Cells to Coagulation

Intact endothelial cells maintain liquid blood flow by actively inhibiting platelet adhesion, coagulation factor activation, and lysing blood clots that may form. Endothelial cells are injured by direct injury or by various cytokines that are produced during inflammation. This leads to increased expression of procoagulant proteins (e.g., tissue factor and vWF) that contribute to thrombus formation. Loss of endothelial integrity exposes underlying vWF and basement membrane, both substrates for platelet aggregation and thrombus formation.

## Platelets

Platelets play a critical role in normal hemostasis. When circulating and nonactivated they are morphologically small, anucleated cells containing several glycoprotein receptors of the integrin family and containing two types of granules:

$\alpha$ -Granules express the adhesion molecule P-selectin on their membranes (Chapter 2) and contain  $\beta_2$ -glycoprotein I, platelet factor 4 (a heparin-binding chemokine), platelet-derived growth factor (PDGF), transforming growth factor- $\alpha$  (TGF- $\alpha$ ). Dense bodies, or  $\delta$  granules, contain adenine nucleotides (ADP and ATP), ionized calcium, and epinephrine.

After vascular injury, platelets encounter ECM constituents (of which collagen is the most important) that are normally not exposed when the endothelial layer is intact. Upon contact with these constituents, platelets undergo three reactions: (1) adhesion and shape change, (2) secretion (release reaction), and (3) aggregation (see Fig. 4-8).

### Platelet Adhesion

Adhesion to ECM is mediated largely via interactions with vWF acting as a bridge between platelet GpIb and exposed collagen (see Fig. 4-8). Although platelets can adhere directly to ECM, vWF-GpIb association is essential to resist shear forces of flowing blood. Genetic deficiencies of vWF (von Willebrand disease; Chapter 12) and GpIb (Bernard-Soulier syndrome) are disorders, highlighting the importance of these interactions. Conversely, failure of the normal proteolytic cleavage of vWF multimers to smaller forms leads to aberrant platelet aggregation in the circulatory system, as seen in *thrombotic thrombocytopenic purpura*, one of the so-called *thrombotic microangiopathies* (see Chapter 12).

### Secretion (Release Reaction)

Secretion of both granule types occurs soon after adhesion. Various agonists can bind specific platelet receptors, initiating an intracellular phosphorylation cascade that leads to degranulation. Release of dense body contents, including ADP and  $\text{Ca}^{2+}$ , is required in the coagulation cascade and ADP is a potent mediator of *platelet aggregation* (platelet aggregation). ADP also causes additional platelet ADP release, amplifying the aggregation process. Finally, release of epinephrine from  $\delta$  granules also contributes to platelet aggregation.

next). ADP also begets additional platelet ADP release, amplifying the aggregation process. Final expression of *phospholipid complexes*, which provide a critical nucleation and binding site for calc *intrinsic clotting pathway* (see later).

### *Platelet Aggregation*

Aggregation follows platelet adhesion and granule release. In addition to ADP, platelet-synthesize also an important stimulus for platelet aggregation. ADP and TXA<sub>2</sub> together drive an autocatalytic enlarging platelet aggregate, the *primary hemostatic plug*. This primary aggregation is reversible. coagulation cascade, the generation of *thrombin*<sub>Rx</sub> results in two processes that make an irreversible a platelet surface receptor (protease-activated receptor, or PAR, see below); in association with A further platelet aggregation. *Platelet contraction* follows, creating an irreversibly fused mass of pla constituting the definitive *secondary hemostatic plug*. Concurrently, *thrombin*<sub>Rx</sub> converts fibrinogen plug, contributing to the overall stability of the clot (see below).

Both erythrocytes and leukocytes are also found in hemostatic plugs; leukocytes adhere to platelet molecules and contribute to the inflammatory response that accompanies thrombosis. *Thrombin*<sub>Rx</sub> neutrophil and monocyte adhesion and by generating chemotactic *fibrin split products* from the cl

### *Importance of Fibrinogen in Platelet Aggregation*

The binding of ADP to its platelet receptor induces a conformational change of the GpIIb-IIIa receptor. Fibrinogen then acts to connect many platelets together to form large aggregates (see Fig. 4-8). This is amply demonstrated by the bleeding disorders that occur in patients with congenitally deficient or clinical recognition of the central role of these GpIIb-IIIa receptors in platelet cross-linking led to the ability to potentially block platelet aggregation-either by interfering with ADP binding, as with clopidogrel, or by blocking with monoclonal antibodies.

### *Interaction of Platelets and Endothelium*

The interplay of platelets and endothelium has a profound impact on the formation of a clot. Prostacyclin (from endothelium) is a vasodilator and inhibits platelet aggregation, whereas TXA<sub>2</sub> is a platelet-derived aggregation and is a potent vasoconstrictor. Effects mediated by PGI<sub>2</sub> and TXA<sub>2</sub> constitute exquisite balance in human platelet function: in the normal state, intravascular platelet aggregation is prevented, whereas in the formation of hemostatic plugs. The clinical use of *aspirin*<sub>Rx</sub> (a cyclooxygenase inhibitor) in patients at risk for thrombosis is an ability to inhibit the synthesis of TXA<sub>2</sub>. In a manner similar to that of PGI<sub>2</sub>, *nitric oxide*<sub>Rx</sub> also acts to inhibit aggregation (see Fig. 4-7).

## **SUMMARY**

### **Platelet Aggregation**

Endothelial injury exposes the underlying basement membrane ECM; platelets adhere to and become activated by binding to vWF through GpIb platelet receptors. Upon activation, they secrete granule products that include calcium (activates coagulation protein cascade, leading to further platelet aggregation and degranulation). Activated platelets also synthesize TXA<sub>2</sub> (which promotes platelet activation and causes vasoconstriction). Activated platelets expose phospholipids that provide an important surface for coagulation-protein activation (see below). ADP and TXA<sub>2</sub> stimulate formation of a primary hemostatic plug by activating platelet GpIIb/IIIa receptors, which facilitate fibrinogen binding and cross-linking. The formation of the definitive hemostatic plug requires the activation of *thrombin*<sub>Rx</sub> to cleave fibrinogen and form polymeric fibrin, which completes the coagulation cascade (see below).

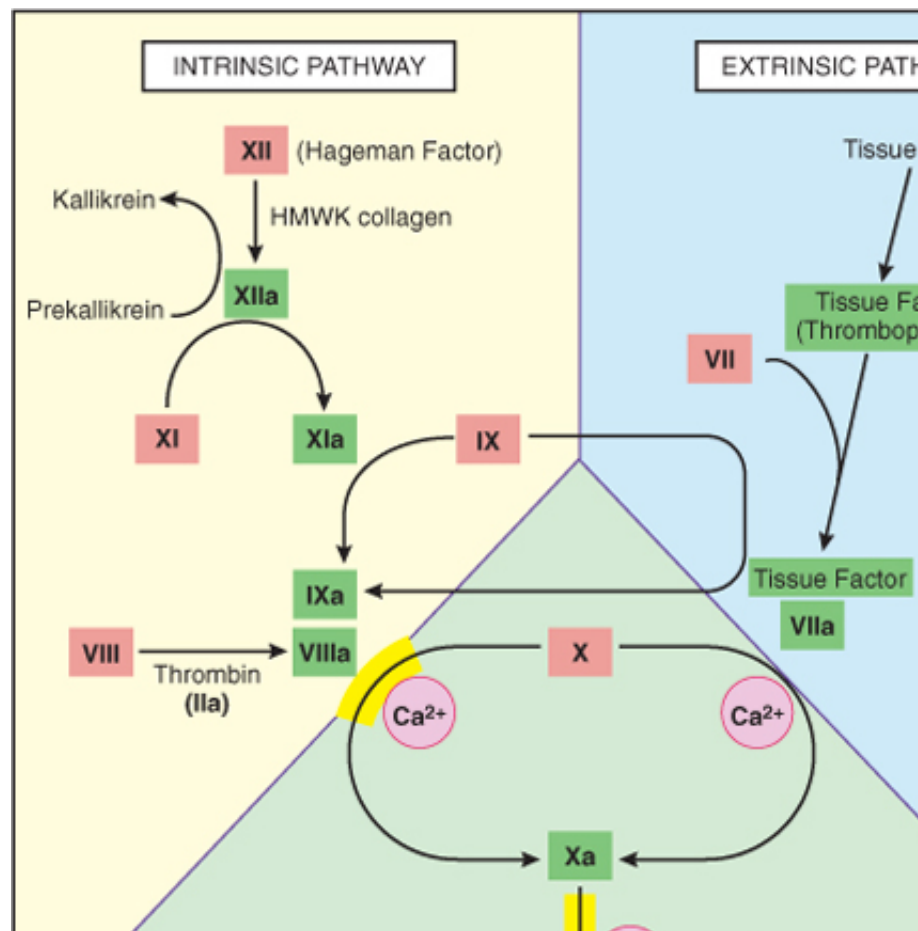
### **Coagulation Cascade**

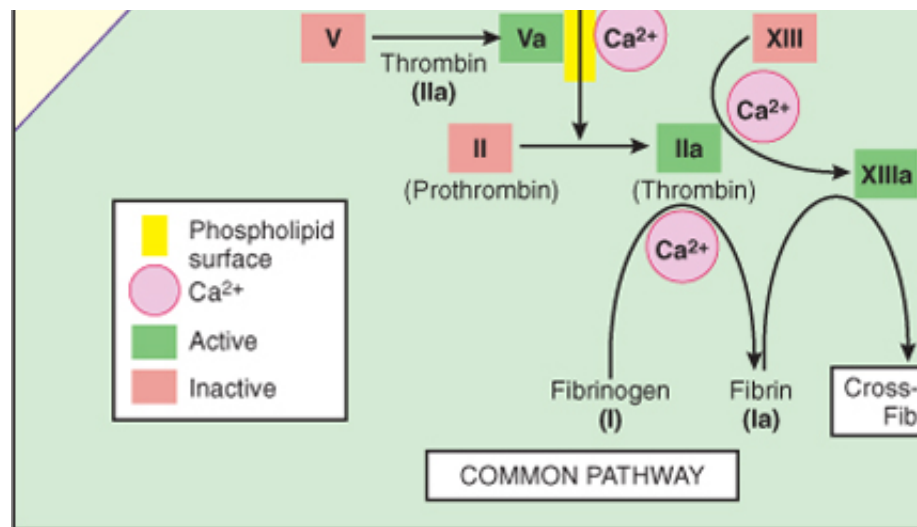
The *coagulation cascade* constitutes the third component of the hemostatic process and is a major



pathways are schematically presented in [Figure 4-9](#); only general principles are discussed here.

The coagulation cascade is essentially an amplifying series of enzymatic conversions; each cleaves an inactive proenzyme into an activated enzyme, eventually culminating in *thrombin*, an important enzyme regulating the coagulation process. *Thrombin* converts the soluble plasma monomers that polymerize into an insoluble gel; this gel encases platelets and other circulating cells to form a hemostatic plug. Fibrin polymers are stabilized by the transglutaminase cross-linking activity. The final pathway results from the assembly of a complex composed of an *enzyme* (activated coagulation factor), and a *cofactor* (reaction accelerator). These components are assembled and held together by *calcium ions*. Thus, clotting tends to remain localized to phospholipid-rich surfaces, for example, on the surface of activated platelets. Two such reactions are the sequential conversion of prothrombin (II) to IIa (*thrombin*) are illustrated in [Figure 4-10](#). Parenthetically, the ability of factors to bind to calcium requires that additional  $\gamma$ -carboxyl groups be enzymatically appended to certain proteins. This reaction requires vitamin K as a cofactor and is antagonized by drugs such as *warfarin*, which can be used in patients who require anticoagulation on a chronic basis—or such as *warfarin*, which can be used to prevent exsanguination. The blood coagulation scheme has been traditionally classified into *extrinsic* and *intrinsic* pathways, with the activation of factor X (see [Fig. 4-9](#)). The extrinsic pathway was so designated because it required an exogenous trigger (originally provided by tissue extracts); the intrinsic pathway required only an endogenous trigger (a thrombogenic surface (even glass would suffice)). However, this classification, although useful, is largely an artifact of *in vitro* testing, since several interconnections exist between the two pathways. The most physiologically relevant of the two in driving coagulation after vascular damage; it is a membrane-bound lipoprotein expressed at sites of injury (see [Fig. 4-9](#)). *thromboplastin* or factor III), a membrane-bound lipoprotein expressed at sites of injury (see [Fig. 4-9](#)). The blood coagulation scheme has been traditionally classified into *extrinsic* and *intrinsic* pathways, with the activation of factor X (see [Fig. 4-9](#)). The extrinsic pathway was so designated because it required an exogenous trigger (originally provided by tissue extracts); the intrinsic pathway required only an endogenous trigger (a thrombogenic surface (even glass would suffice)). However, this classification, although useful, is largely an artifact of *in vitro* testing, since several interconnections exist between the two pathways. The most physiologically relevant of the two in driving coagulation after vascular damage; it is a membrane-bound lipoprotein expressed at sites of injury (see [Fig. 4-9](#)). *thromboplastin* or factor III), a membrane-bound lipoprotein expressed at sites of injury (see [Fig. 4-9](#)).





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Figure 4-9 The classical coagulation cascade. Note the common link between the intrinsic and extrinsic pathways. Red boxes represent inactive molecules; activated factors are indicated with a lower-case a and a green box. HMWK, high molecular weight kininogen; TAFI, tissue activating factor. See the inhibitory anticoagulant pathways (see Figs. 4-7 and 4-12).

The PT assay screens for the activity of the proteins in the extrinsic pathway (factors VII, X, II, V, and tissue factor) to a patient's citrated plasma (sodium citrate chelates any calcium present and prevents the clotting reaction). The clotting reaction is started by adding exogenous calcium, and the time to fibrin clot formation (usually 12-15 seconds) is recorded. In addition to its value as a screening assay for the normal activity of the proteins, the PT is sensitive to the effects of coumadin. It is therefore used to monitor the efficacy of coumadin anticoagulation, which is maintained between 2 and 3 in patients receiving coumadin.

The PTT assay screens for the activity of the proteins in the intrinsic pathway (factors XII, XI, IX, and X) to a patient's citrated plasma, and the time to fibrin clot formation (usually 28-35 seconds) is recorded. In addition to its value in screening for the normal activity of the proteins, the PTT assay's sensitivity to the effects of heparin makes it useful to monitor the efficacy of heparin therapy.

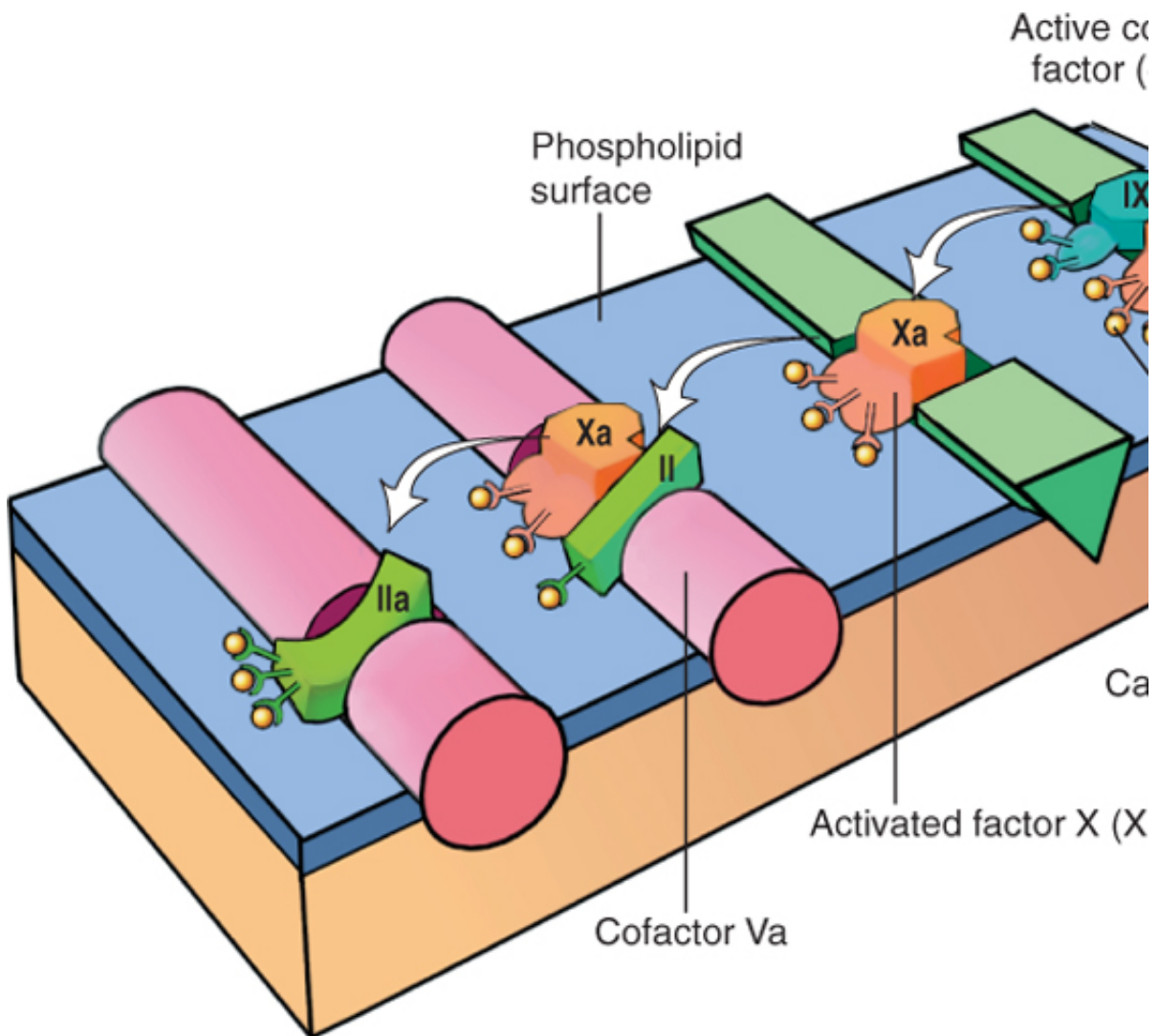
In addition to catalyzing the final steps in the coagulation cascade, **thrombin** exerts a wide range of effects on the vasculature and inflammatory milieu; it even actively participates in limiting the extent of thrombosis. These thrombin-mediated effects occur through protease-activated receptors belonging to a family of G-protein-coupled receptors (see Fig. 4-7). Once activated, the coagulation cascade must be restricted to prevent runaway clotting of the entire vascular tree. In addition to the restriction of factor activation to the surface of phospholipids, three categories of natural anticoagulants function to control clotting: *antithrombin*, *tissue factor pathway inhibitor* (TFPI), and *protein C*.

Antithrombins (e.g., antithrombin III) inhibit the activity of **thrombin** and other serine proteases, including **XIIIa**. Antithrombin III is activated by binding to heparin-like molecules on endothelial cells. Administering heparin in clinical situations to reduce thrombotic activity (see Fig. 4-7) is largely accomplished by the enzymatic activity of *plasmin*, which breaks down fibrin and fibrinogen. The resulting *fibrin split products* (FSPs, or *fibrin degradation products*) can also act as anticoagulants. Protein C activation by **thrombin** and **protein S** is a cofactor for protein C activity (see Fig. 4-7). TFPI is a protein secreted by endothelial cells that inactivates factor **Xa** and tissue factor-VIIa complexes (see Fig. 4-7).

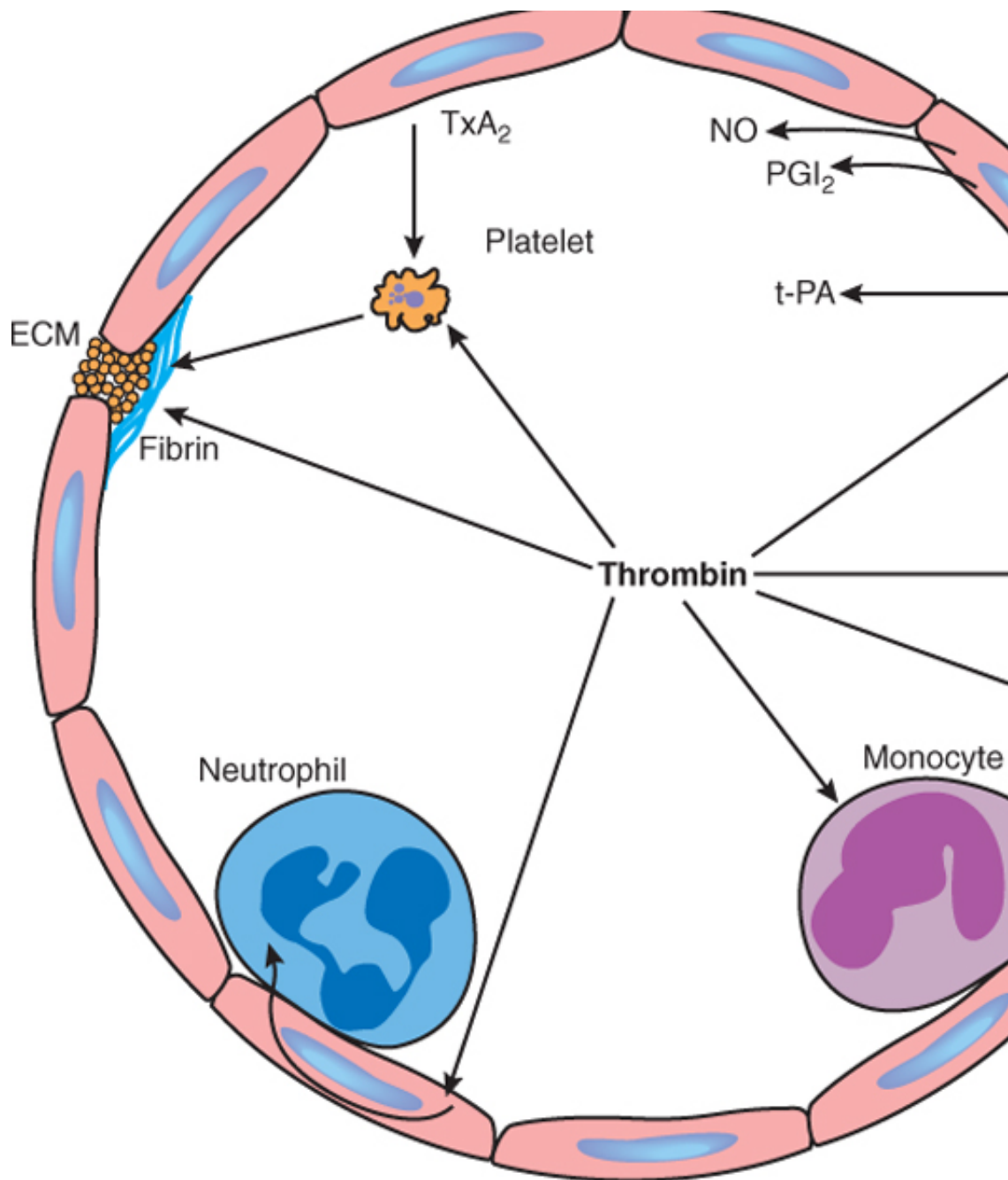
Activation of the clotting cascade also sets into motion a *fibrinolytic cascade* that moderates the extent of clotting. This process is largely accomplished by the enzymatic activity of *plasmin*, which breaks down fibrin and fibrinogen. The resulting *fibrin split products* (FSPs, or *fibrin degradation products*) can also act as anticoagulants. In clinical laboratories, elevated levels of FSPs (clinical laboratories most frequently measure the fibrinogen level) are associated with abnormal thrombotic states including disseminated intra-vascular coagulation (DIC), deep vein thrombosis, and pulmonary embolism.

thromboembolism (described in detail later).

Plasmin is generated by enzymatic degradation of the inactive circulating precursor *plasminogen* by plasminogen activators (PAs; see Fig. 4-12). The most important of the PAs is tissue plasminogen activator (tPA) released by endothelial cells and is most active when attached to fibrin. The affinity for fibrin makes tPA largely confine fibrinolytic activity to sites of recent thrombosis. *Urokinase-like PA (u-PA)* is found in various tissues; it can activate plasmin in the fluid phase. Finally, plasminogen can be cleaved by the product *streptokinase*, an activity that may be clinically significant in various bacterial infections. In the blood component, the activity of plasmin is also tightly restricted. To prevent excess plasmin from acting elsewhere in the body, free plasmin rapidly forms a complex with circulating  $\alpha_2$ -antiplasmin (Fig. 4-12). Endothelial cells further modulate the coagulation/anticoagulation balance by releasing an overall procoagulation effect (see Fig. 4-12). The PAs are increased by certain cytokines during intravascular thrombosis accompanying severe inflammation.

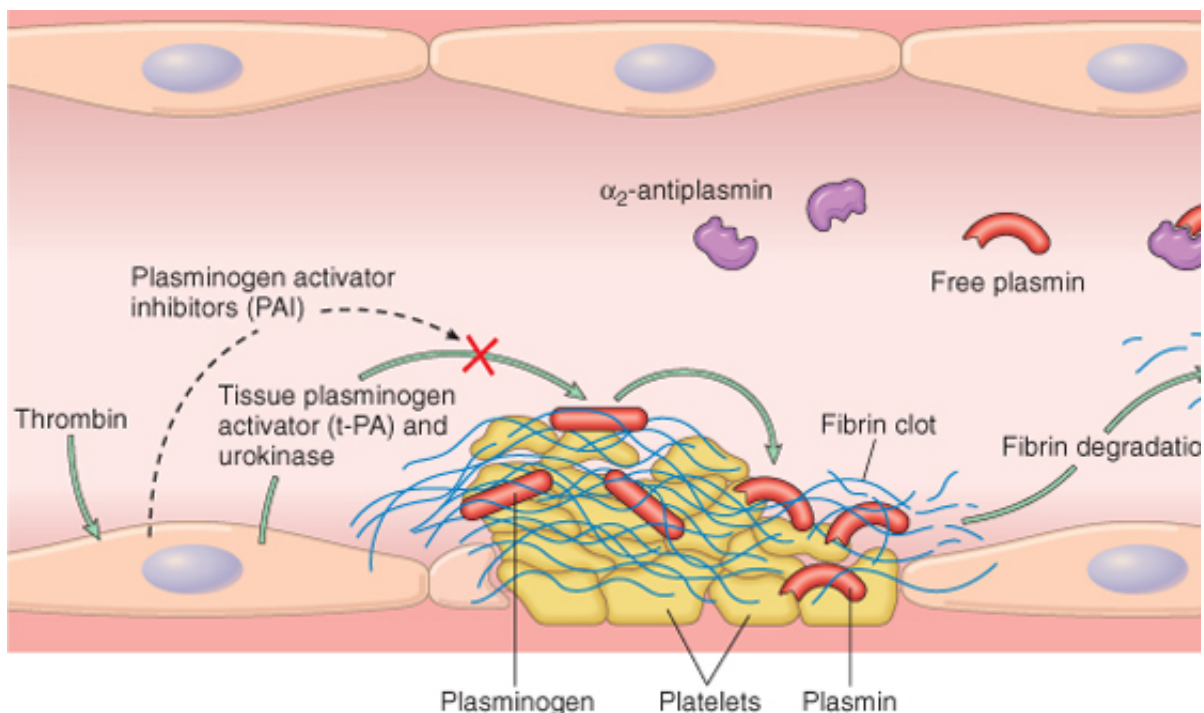


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 Figure 4-10 Sequential conversion of factor X to factor Xa, followed by factor II (prothrombin) to factor IIa (thrombin). The reaction requires factor IXa (enzyme), a substrate (factor X), and a reaction accelerator (factor VIIIa), all assembled on a platelet surface. Activated factor Xa becomes the enzyme part of the cascade, converting the prothrombin substrate to IIa using factor Va as the reaction accelerator. (Modified from Mahan et al, Med 4:217, 1984.)



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 Figure 4-11 Role of **thrombin** in hemostasis and cellular activation. **Thrombin** plays a critical role in generating fibrin and activation of factor XIII. Through protease-activated receptors (PARs, see text), **thrombin** also modulate platelet aggregation and  $\text{TxA}_2$  secretion and can activate endothelium to generate leukocyte adhesion molecule a  $\text{PGI}_2$ , and cytokine (PDGF) mediators. **Thrombin** also directly activates leukocytes. ECM, extracellular matrix; factor;  $\text{PGI}_2$ , prostacyclin;  $\text{TxA}_2$ , thromboxane  $\text{A}_2$ ; t-PA, tissue plasminogen activator. See Figure 4-7 for additional such as antithrombin III and thrombomodulin. (Courtesy of Shaun Coughlin, MD, PhD, Cardiovascular Research Ir modified with permission.)





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Figure 4-12 The fibrinolytic system, illustrating various plasminogen activators and ir

## SUMMARY

### Coagulation Factors

Coagulation occurs via the sequential enzymatic conversion of a cascade of synthesized proteins. Tissue factor elaborated at sites of injury is the most important in the coagulation cascade; at the final stage of coagulation, **thrombin** converts fibrinogen to fibrin, which helps to form the definitive hemostatic plug. Coagulation is normally initiated by vascular injury by:

Limiting enzymatic activation to phospholipid complexes provided by anticoagulants elaborated at sites of endothelial injury or during activation of the cascade. Induction of fibrinolytic pathways involving plasmin through t-PA and urokinase.

## Thrombosis

Having discussed the process of normal hemostasis, we can now turn our attention to the dysregulation of hemostasis and the process of thrombosis.

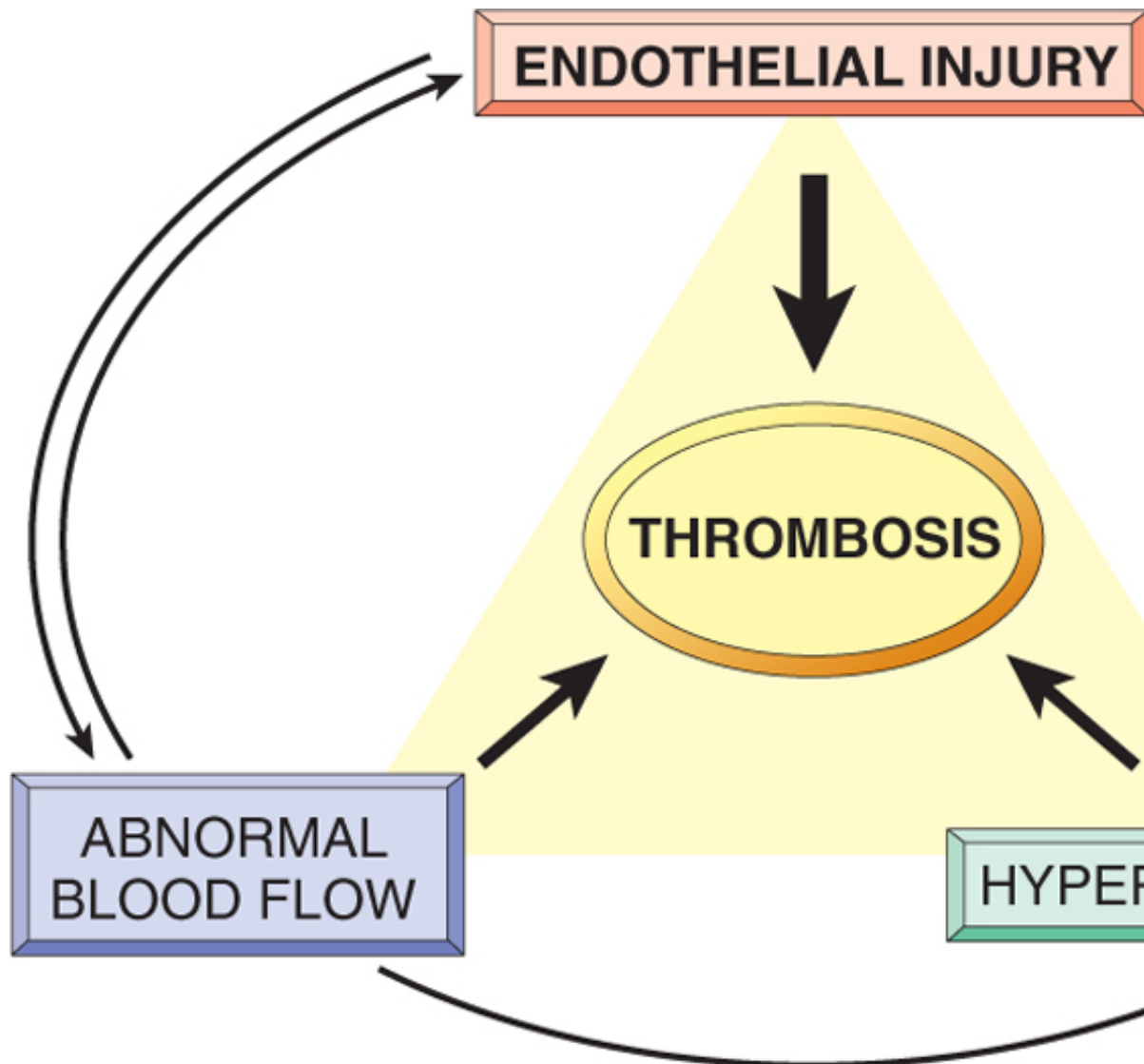
### Pathogenesis

There are three primary influences on thrombus formation (called *Virchow's triad*): (1) endothelial injury, (2) abnormal blood flow, and (3) blood hypercoagulability (Fig. 4-13).

### Endothelial Injury

This is a dominant influence, since endothelial loss by itself can lead to thrombosis. It is particularly important in the heart or in the arterial circulation, where the normally high flow rates might otherwise prevent the adhesion or diluting of coagulation factors. Thus, thrombus formation within the cardiac chambers (e.g., in myocardial infarction), over ulcerated plaques in atherosclerotic arteries, or at sites of traumatic or surgical injury is largely a function of endothelial injury. Clearly, physical loss of endothelium leads to exposure of the underlying subendothelial tissue, which is highly thrombogenic.

platelets, release of tissue factor, and local depletion of PGI<sub>2</sub> and plasminogen activators. However, endothelium need not be denuded or physically disrupted to contribute to the development of thrombosis; any alteration in the prothrombotic and antithrombotic activities of endothelium can influence local clotting events (e.g., endothelium may elaborate greater amounts of procoagulant factors (e.g., platelet adhesion molecules, tissue factor) or may synthesize fewer anticoagulant effectors (e.g., thrombomodulin, PGI<sub>2</sub>, t-PA). Significant endothelial dysfunction (e.g., absence of endothelial cell loss) may occur with hypertension, turbulent flow over scarred valves, or atherosclerosis. Even relatively subtle influences, such as homocystinuria, hypercholesterolemia, radiation, or proinflammatory cytokines, may be sources of endothelial dysfunction.



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 Figure 4-13 Virchow's triad in thrombosis. Integrity of endothelium is the most important factor. Injury to endothelium increases local coagulability. Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury. The factors may interact to promote thrombus formation.

#### Alterations in Normal Blood Flow

**Turbulence** contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, creating countercurrents and local pockets of stasis; **stasis** is a major contributor to the development of venous thrombosis. In **laminar** flow, such that platelets flow centrally in the vessel lumen, separated from the endothelium by the boundary layer. Stasis and turbulence therefore:

Disrupt laminar flow and bring platelets into contact with the endothelium  
Prevent dilution of blood  
Retard the inflow of clotting factor inhibitors and permit the buildup of thrombi  
Promote local thrombosis, leukocyte adhesion, etc.

Turbulence and stasis contribute to thrombosis in several clinical settings. Ulcerated atherosclerotic subendothelial ECM but also cause turbulence. Abnormal aortic and arterial dilations, called *aneurysms*, are consequently a fertile site for thrombosis (Chapter 10). Acute myocardial infarction results in focal remodeling after more remote infarction can lead to aneurysm formation. In both cases cardiac malformations cause the local blood stasis (Chapter 11). Mitral valve stenosis (e.g., after rheumatic heart disease) results in atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for development of thrombi (such as *polycythemia*; Chapter 12) increase resistance to flow and cause small vessel stasis; the (Chapter 12) cause vascular occlusions, with the resultant stasis also predisposing to thrombosis.

### Hypercoagulability

Hypercoagulability generally contributes less frequently to thrombotic states but is nevertheless an important factor. It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis, a primary (inherited) and secondary (acquired) disorders (Table 4-2).

Primary (inherited) hypercoagulable states. Of the inherited causes of hypercoagulability, mutations in the prothrombin gene are the most common: Secondary (acquired) hypercoagulable states. The pathogenesis of *acquired thrombotic diatheses* is frequently multifactorial and is therefore variable. In some situations (e.g., cardiac failure or trauma), stasis or vascular injury may be most important. With oral contraceptive use and the hyperestrogenic state of pregnancy, probably related to increased levels of coagulation factors and reduced synthesis of antithrombin III. In disseminated cancers, release of procoagulant substances predisposes to thrombosis. The hypercoagulability seen with advancing age has been attributed to decreased fibrinolysis and reduced endothelial PGI<sub>2</sub> release. Smoking and obesity promote hypercoagulability by

**Table 4-2. Hypercoagulable States**

<b>Primary (Genetic)</b>
Common
Mutation in factor V gene (factor V Leiden)
Mutation in prothrombin gene
Mutation in methyltetrahydrofolate gene
Rare
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Very rare
Fibrinolysis defects
<b>Secondary (Acquired)</b>
High risk for thrombosis
Prolonged bedrest or immobilization
Myocardial infarction
Atrial fibrillation
Tissue damage (surgery, fracture, burns)
Cancer
Prosthetic cardiac valves
Disseminated intravascular coagulation

Heparin-induced thrombocytopenia
Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)
Lower risk for thrombosis
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states (pregnancy)
Oral contraceptive use
Sickle cell anemia
Smoking

Among the acquired causes of thrombotic diathesis, the *heparin-induced thrombocytopenia (HIT) syndrome* (previously called the *lupus anticoagulant syndrome*) deserve special mention.

Seen in as many as 5% of the population, the HIT syndrome occurs when administration of heparin (an anticoagulation) induces autoantibodies to complexes of heparin and a platelet membrane protein. This antibody binds to similar complexes present on platelet and endothelial surfaces, resulting in platelet cell injury, and a net *prothrombotic state*. The occurrence of HIT syndrome can be reduced by using heparin preparations that retain anticoagulant activity but do not interact with platelets; these preparations have a prolonged serum half-life. Antiphospholipid antibody syndrome has protean manifestations including repeated miscarriages, cardiac valve vegetations, and thrombocytopenia; it is associated with antibodies to anionic phospholipids (e.g., cardiolipin) or more accurately plasma protein antigens that are associated with phospholipids (e.g., prothrombin). In vivo these antibodies induce a *hypercoagulable state*, by interfering with endothelial cell production of PGI<sub>2</sub>. However, in vitro (in the absence of platelets) they merely interfere with phospholipid complex assembly and thus inhibit coagulation (hence the name). Patients with antibodies to cardiolipins also have a false-positive serologic test for syphilis, because cardiolipin is embedded in cardiolipin.

There are two types of antiphospholipid antibody syndrome. Many patients have *secondary* antiphospholipid antibody syndrome, a well-defined autoimmune disease, such as systemic lupus erythematosus ([Chapter 5](#)). In contrast, others have a *primary* antiphospholipid antibody syndrome, a hypercoagulable state without evidence of other autoimmune disorder ([Chapter 5](#)). Patients with antiphospholipid antibody syndrome are at increased risk of thrombosis (in one series). Therapy involves anticoagulation, with immunosuppression in refractory cases. If patients with antiphospholipid antibody syndrome are associated with thrombotic diatheses, they have also been identified in 5% to 15% of cases of thrombotic thrombocytopenic syndrome that they may be necessary but not sufficient to cause full-blown antiphospholipid antibody syndrome.

### Morphology

Thrombi can develop anywhere in the cardiovascular system (e.g., in cardiac chambers, arteries, veins, or capillaries). The size and shape of a thrombus depend on the site of formation. Arterial or cardiac thrombi typically begin at sites of endothelial injury or turbulence of flow. Venous thrombi characteristically occur at sites of stasis. Thrombi are focally attached to the underlying vessel wall. Arterial thrombi tend to grow in a retrograde direction from the point of attachment, while venous thrombi extend in the direction of blood flow (thus both tend to propagate toward the heart). The attachment of a thrombus tends to be poorly attached and therefore prone to fragmentation, generally at the point of attachment.

Thrombi can have grossly (and microscopically) apparent laminations called **lines of Zahn**, consisting of pale platelet and fibrin layers alternating with darker erythrocyte-rich layers. Such laminations indicate that they represent thrombosis in the setting of flowing blood; their presence can therefore distinguish antemortem thrombosis from the bland nonlaminated clots that occur in stasis (see also below). Although such lines are typically not as apparent in veins or small arteries, they are more apparent in sluggish venous flow usually resemble statically coagulated blood, careful dissection reveals ill-defined laminations.

Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi**. They are often associated with myocardial contraction (resulting from arrhythmias, dilated cardiomyopathy, or myocardial infarction). Myocardial infarction (caused by myocarditis, catheter trauma) promotes cardiac thrombosis.



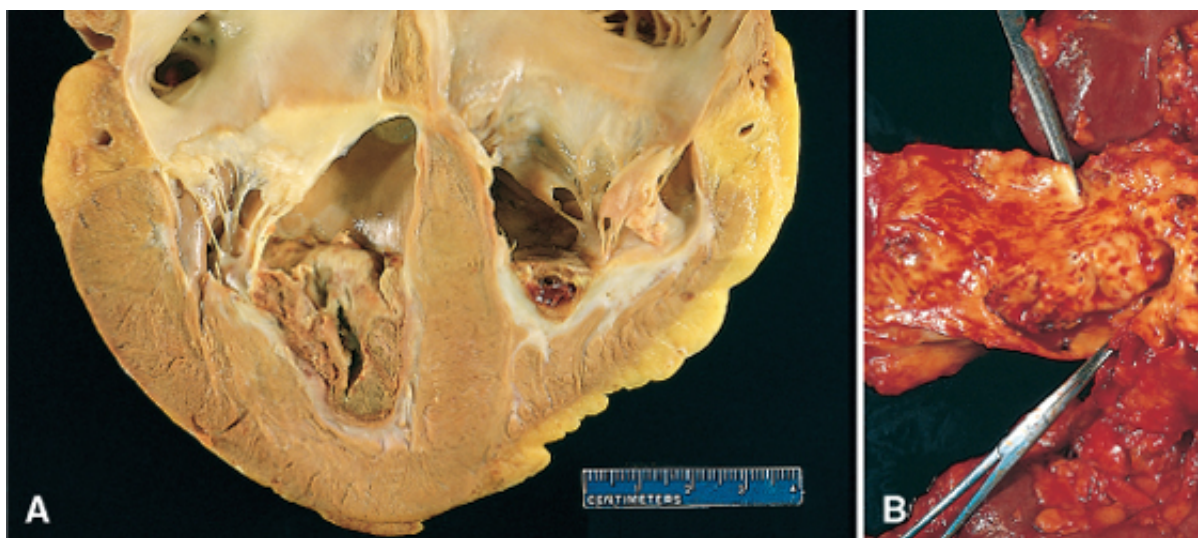
...while ulcerated atherosclerotic plaques and aneurysmal dilation promote aortic thrombosis.

**Arterial thrombi** are frequently occlusive and are produced by platelet and coagulation factors. They typically consist of a friable meshwork of platelets, fibrin, erythrocytes, and degenerating leukocytes. Arterial thrombi are usually superimposed on an atherosclerotic plaque, other vascular injury may be involved.

**Venous thrombosis** (phlebothrombosis) is almost invariably occlusive, and the thrombus fills the lumen; venous thrombosis is largely the result of activation of the coagulation cascade. Platelets play a secondary role. Because these thrombi form in the sluggish venous circulation, they contain more enmeshed erythrocytes and are therefore called red, or stasis, thrombi. Venous thrombi in the lower extremities are most commonly affected (90% of venous thromboses); however, they can also occur in the upper extremities, periprostatic plexus, or ovarian and periuterine vein. In certain circumstances they may be found in the dural sinuses, portal vein, or hepatic vein.

**Postmortem clots** can sometimes be mistaken at autopsy for venous thrombi. However, "postmortem clots" are gelatinous, with a dark red dependent portion where red cells have settled and a pale yellow "chicken fat" supernatant, and they are usually not attached to the underlying vessel wall. Venous thrombi are firmer and are focally attached, and sectioning reveals strands of gray fibrin.

Thrombi on heart valves are called **vegetations**. Bacterial or fungal blood-borne infection can damage the valve, subsequently leading to large thrombotic masses (infective endocarditis). Vegetations can also develop on noninfected valves in hypercoagulable states, so-called **thrombotic endocarditis** (Chapter 11). Less commonly, sterile, verrucous endocarditis (Libman-Sacks endocarditis) can occur in the setting of systemic lupus erythematosus (Chapter 5).



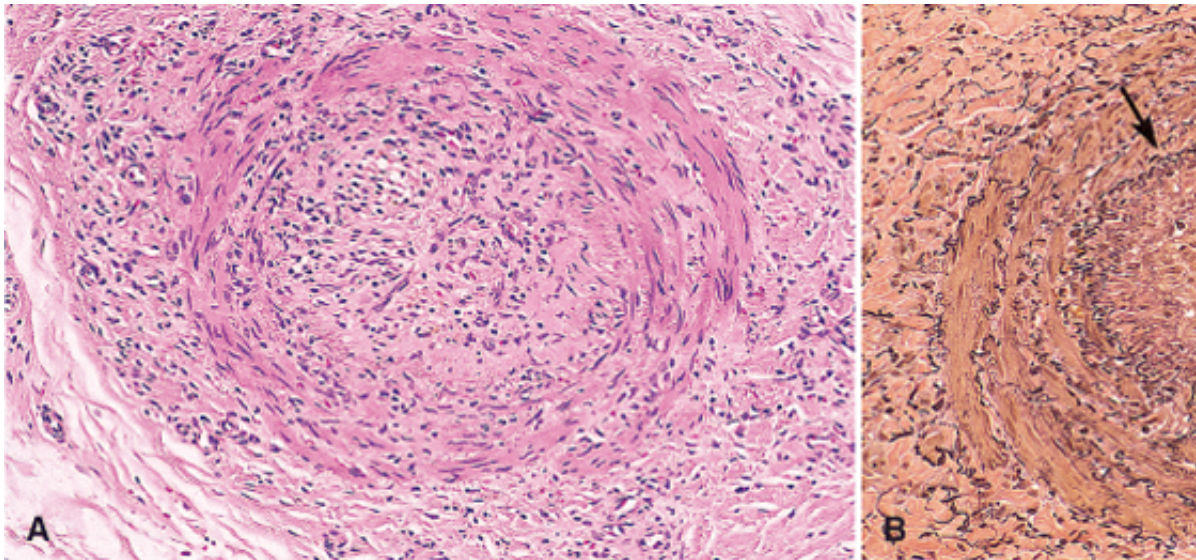
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Figure 4-14 Mural thrombi. **A**, Thrombus in the left and right ventricular apices, overlying white fibrous scar. **B**, Large mural thrombus in a blood vessel. Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the aorta.

### Fate of the Thrombus

If a patient survives the initial thrombosis, in the ensuing days or weeks thrombi undergo some changes.

**Propagation.** Thrombi accumulate additional platelets and fibrin, eventually causing vessel occlusion. They may also dislodge or fragment and are transported elsewhere in the vasculature. **Dissolution.** Thrombi may be dissolved by plasmin activity. **Organization and recanalization.** Thrombi induce inflammation and fibrosis (organization), which may result in re-establishing some degree of flow, or they can be incorporated into a thickened vessel wall.

Propagation was discussed above, and embolization is covered in greater detail below. Dissolution which leads to rapid shrinkage and even total lysis of *recent* thrombi. With older thrombi, extensive thrombus substantially more resistant to proteolysis, and lysis is ineffectual. This is clinically significant of fibrinolytic agents (e.g., t-PA in the setting of acute coronary thrombosis) is generally effective for dissolution.



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Figure 4-15 Low-power view of an artery with an old thrombus. **A**, H&E-stained section. **B**, Stain for elastic tissue. elastic lamina (arrows) and is totally filled with organized thrombus, now punctuated by a number of re

Older thrombi become *organized* by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts (Figure 15). Capillary channels are eventually formed that, to a limited extent, can create conduits along the vessel wall to establish the continuity of the original lumen. Although the channels may not successfully restore the vessel lumen, recanalization can potentially convert a thrombus into a vascularized mass of connective tissue that remains as a subendothelial swelling. Eventually, with contraction of the vessel wall, the thrombus remains to mark the original thrombus site. Occasionally, instead of organizing, the center of a thrombus may undergo liquefaction, presumably because of the release of lysosomal enzymes from trapped leukocytes and platelets.

#### *Clinical Correlations: Venous versus Arterial Thrombosis*

Thrombi are significant because *they cause obstruction of arteries and veins and are potential sources of emboli*. The importance depends on the site of thrombosis. Venous thrombi can cause congestion and edema in the lower extremities, but they are most worrisome for their capacity to embolize to the lungs and cause death (see below). Arterial thrombi can cause cerebral vessels) is much more significant clinically.

#### **Venous Thrombosis (Phlebothrombosis)**

Most venous thrombi occur in the superficial or deep veins of the leg. Superficial venous thrombi occur particularly when there are varicosities. Such superficial thrombi can cause local congestion, swelling, and pain along the course of the involved vein, but they rarely embolize. Nevertheless, the local edema and impaired circulation can lead to infections from minor trauma and to the development of *varicose ulcers*. Deep thrombi in the knee joint (e.g., popliteal, femoral, and iliac veins) are more serious because they may embolize to the lungs and cause edema, the venous obstruction may be rapidly offset by collateral bypass channels. Consequently, deep venous thrombosis is entirely asymptomatic in approximately 50% of patients and are recognized in retrospect only after

Deep venous thrombosis can occur with stasis or in a variety of hypercoagulable states, as described below.

failure is an obvious reason for stasis in the venous circulation. Trauma, surgery, and burns usual injury to vessels, release of procoagulant substances from tissues, and/or reduced t-PA activity. T the thrombotic propensity of peripartum and postpartum states; in addition to the potential for amr during parturition (see below), late pregnancy and the postpartum period are associated with hype procoagulant release is largely responsible for the increased risk of thromboembolic phenomena : *migratory thrombophlebitis*, or *Trousseau's syndrome*). Regardless of the specific clinical setting, immobilization increase the risk of deep venous thrombosis because reduced physical activity dir the lower leg and so slows venous return.

### Cardiac and Arterial Thrombosis

*Atherosclerosis* is a major initiator of thromboses, because it is associated with loss of endothelial Fig. 4-14B). Cardiac mural thrombi can occur in the setting of myocardial infarction related to dysl damage to the adjacent endocardium (see Fig. 4-14A). *Rheumatic heart disease* (Chapter 11) car valve stenosis, followed by left atrial dilation and concurrent atrial fibrillation. In addition to the obs mural thrombi can also embolize peripherally. Virtually any tissue can be affected, but brain, kidn because of their large volume of blood flow.

### SUMMARY Thrombosis

Thrombus development depends on the relative contribution of the compon:  
Endothelial injury (e.g., by toxins, hypertension, inflammation, or met  
blood flow - stasis or turbulence (e.g., due to aneurysms, atheroscler  
plaque)Hypercoagulability, which can be either primary (e.g., factor \  
prothrombin synthesis, antithrombin III deficiency) or secondary (e.g.  
malignancy)

Thrombi may propagate, resolve, become organized, or embolize. Thrombo:  
local vascular occlusion or by distal embolization.







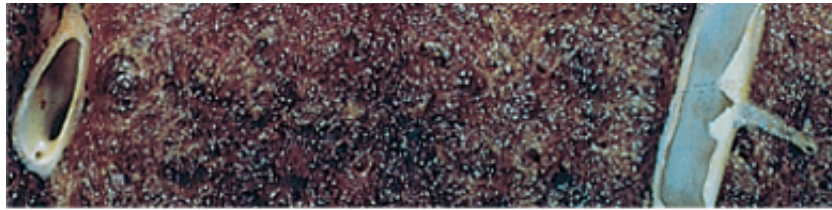
## EMBOLISM

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood. Virtually 99% of all emboli represent some part of a dislodged thrombus, hence the term *thromboembolism*. Other types include fat droplets, bubbles of air or nitrogen, atherosclerotic debris (*cholesterol emboli*), tumor fragments such as bullets. However, unless otherwise specified, an embolism should be considered to be a thrombus that has lodged in vessels too small to permit further passage, resulting in partial or complete vascular occlusion. Thromboembolism includes ischemic necrosis (*infarction*) of downstream tissue. Depending on the site of the embolism in the vascular tree; the clinical outcomes are best understood from the standpoint of whether emboli are arterial or venous circulations.

### Pulmonary Thromboembolism







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Figure 4-16 Embolus derived from a lower extremity deep venous thrombosis and now impacted

Pulmonary embolism has an incidence of 20 to 25 per 100,000 hospitalized patients. Although the assessed at autopsy) has declined from 6% to 2% over the last quarter century, pulmonary embolism remains a leading cause of death in the United States. In more than 95% of cases, venous emboli originate from deep leg vein thromboses (described above). They are carried through progressively larger channels and pass through the pulmonary vasculature. Depending on the size of the embolus, it may occlude the main pulmonary artery (saddle embolus), or pass out into the smaller, branching arterioles (Fig. 4-16). Frequently, there is a shower of smaller emboli from a single large thrombus; in general, *the patient who has had a pulmonary embolism is more likely to have more than one*. Rarely, an embolus can pass through an interatrial or interventricular defect, thereby causing a paradoxical embolism. The following is an overview of pulmonary emboli; see Chapter 13 for a more detailed discussion.

Most pulmonary emboli (60% to 80%) are clinically silent because they are small. They eventually become incorporated into the vascular wall; in some cases, organization of the thromboembolus leads to recanalization. Sudden death, right ventricular failure (*cor pulmonale*), or cardiovascular collapse occur when large emboli obstruct the pulmonary circulation. Embolic obstruction of medium-sized arteries can cause pulmonary infarction because the lung has a dual blood supply and the intact bronchial arteries supply the area. However, a similar embolus in the setting of left-sided cardiac failure (and resultant pulmonary congestion) may result in a large infarct. Embolic obstruction of small end-arteriolar pulmonary branches can cause segmental infarction. Many emboli occurring over a period of time may cause pulmonary hypertension.

### Systemic Thromboembolism

Systemic thromboembolism refers to emboli in the arterial circulation. Most (80%) arise from intracardiac thrombi, which are associated with left ventricular wall infarcts and another quarter with dilated left atria (e.g., secondary to mitral stenosis). The remainder originate from aortic aneurysms, thrombi on ulcerated atherosclerotic plaques, or fragments of atherosclerotic plaques (Fig. 4-17). A very small fraction of systemic emboli appear to arise in veins but end up in the arterial circulation. These are called *paradoxical emboli*. In contrast to venous emboli, which tend to lodge primarily in the lower extremities, emboli can travel to a wide variety of sites; the site of arrest depends on the point of origin of the embolus and the flow through the downstream tissues. The major sites for arteriolar embolization are the lower extremities, the intestines, kidneys, and spleen affected to a lesser extent. The consequences of embolization include tissue ischemia, caliber of the occluded vessel, and the collateral blood supply; in general, arterial emboli cause more severe tissue damage than venous emboli.

### Fat Embolism

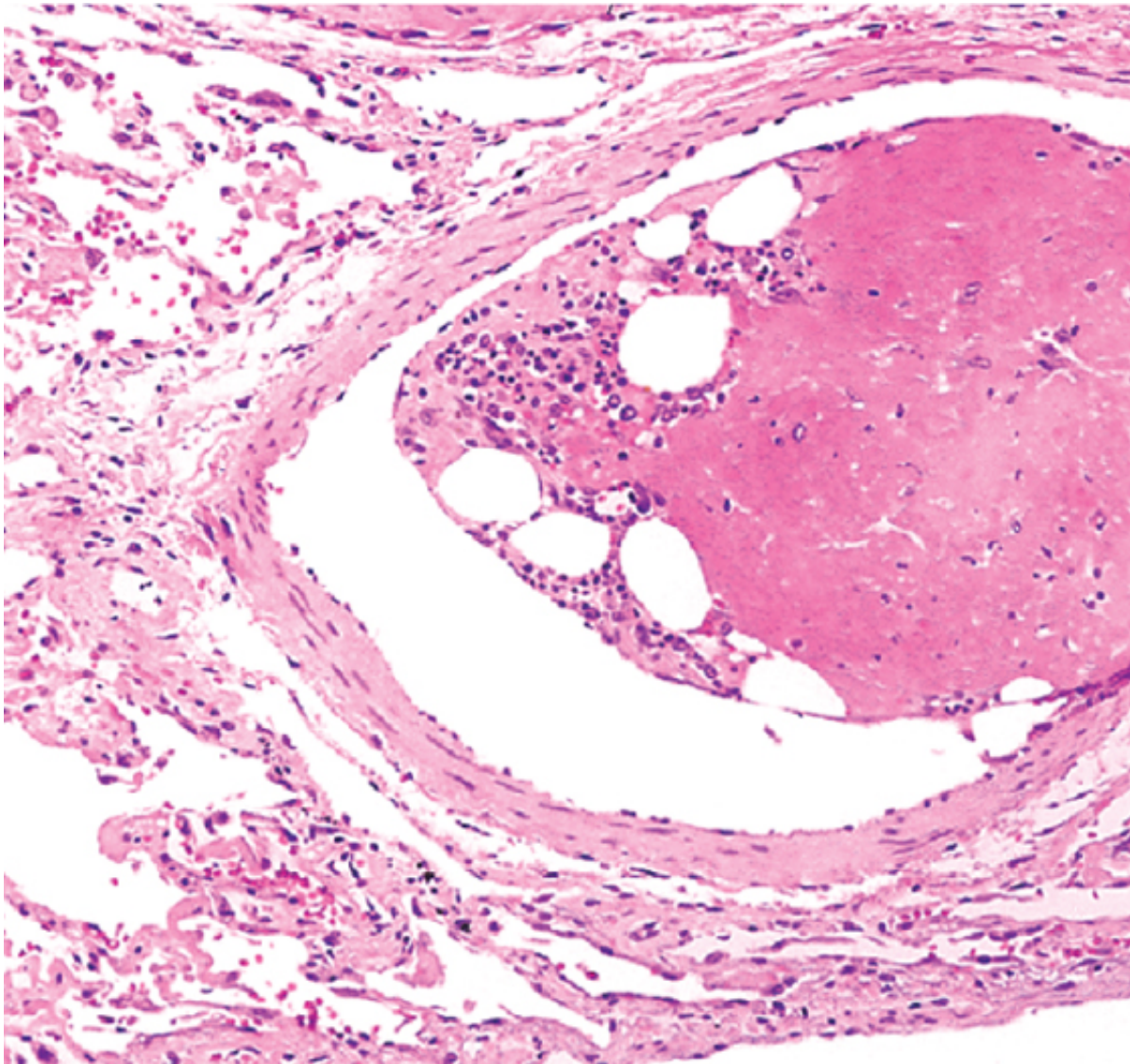
Microscopic fat globules can be found in the circulation after fractures of long bones (which contain marrow). Fat enters the circulation by rupture of the marrow vascular sinusoids or rupture of venule walls. Fat embolism occurs in some 90% of individuals with severe skeletal injuries (Fig. 4-17), few have clinical findings. *Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, and thrombocytopenia; it is fatal in about 10% of cases.* Typically, the symptoms appear 1 to 3 days after the injury. Symptoms include tachypnea, dyspnea, and tachycardia. Neurologic symptoms include irritability and restlessness, and

The pathogenesis of fat emboli syndrome probably involves both mechanical obstruction and biochemical injury to the pulmonary and cerebral microvasculature; vascular occlusion is aggravated by local platelet and endothelial cell activation and further exacerbated by free fatty acid release from the fat globules, causing local toxic injury to endothelial cells and recruitment of granulocytes (with free radical, protease, and eicosanoid release; Chapter 2) comp

are dissolved out of tissue preparations by the solvents routinely used in paraffin embedding, the microglobules (i.e., in the absence of accompanying marrow) typically requires specialized techniques and special stains.

### Air Embolism

Gas bubbles within the circulation can obstruct vascular flow (and cause distal ischemic injury) and can be fatal. Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury. In some cases, air emboli are required to produce a clinical effect; bubbles can coalesce to form frothy masses sufficiently large to obstruct flow.



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Figure 4-17 Bone marrow embolus in the pulmonary circulation. The cellular elements on the left side of the embolus are blood cells. The cleared vacuoles represent marrow fat. The relatively uniform red area on the right of the embolus is the cellular component of the marrow.

A particular form of gas embolism, called *decompression sickness*, occurs when individuals are exposed to a rapid decrease in atmospheric pressure. Scuba and deep-sea divers, and underwater construction workers are at risk. When a person ascends (depressurizes) too rapidly, the nitrogen expands in the tissues and bubbles out of solution. This can induce focal ischemia in a number of tissues, including brain and heart. The rapid formation of gas bubbles in the blood can also cause a gas embolism.

supporting tissues in and about joints is responsible for the painful condition called *the bends* (so individuals characteristically arched their backs in a manner reminiscent of a then-popular women the lungs, gas bubbles in the vasculature cause edema, hemorrhages, and focal atelectasis or em called the *chokes*. A more chronic form of decompression sickness is called *caisson disease*, wh leads to multiple foci of ischemic necrosis; the heads of the femurs, tibias, and humeri are most c

Treating acute decompression sickness requires placing the affected individual in a compression and force the gas bubbles back into solution. Subsequent slow decompression theoretically permi the gases so that obstructive bubbles do not re-form.

### **Amniotic Fluid Embolism**

Amniotic fluid embolism is a grave but fortunately uncommon complication of labor and the immec deliveries). It has a mortality rate in excess of 20% to 40%. The onset is characterized by sudden hypotensive shock, followed by seizures and coma. If the patient survives the initial crisis, pulmon (in half the patients) disseminated intravascular coagulation (DIC), due to release of thrombogenic

The underlying cause is entry of amniotic fluid (and its contents) into the maternal circulation via a rupture of uterine veins. Classically, there is marked pulmonary edema and diffuse alveolar dama microcirculation containing squamous cells shed from fetal skin, lanugo hair, fat from vernix casec respiratory or gastrointestinal tracts. Systemic fibrin thrombi indicate the onset of DIC.

### **SUMMARY Embolism**

An embolus is any detached solid, liquid, or gaseous mass carried by the bl its origin; the vast majority are part of a dislodged thrombus. Pulmonary emb lower extremity deep vein thrombosis; their effect (sudden death, right heart hemorrhage, or infarction) depends on the size of the embolus. Systemic em cardiac mural or valvular thrombi, aortic aneurysms, or atherosclerotic plaqu causes tissue infarction depends on the site of embolization and collateral c





## INFARCTION

An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue. Tissue infarction is a common and extremely important cause of clinical illness. More than half of all deaths in the United States are caused by cardiovascular disease, and most of these are attributable to myocardial or cerebral infarction. Pulmonary infarction is a common complication in several clinical settings, bowel infarction is frequently fatal, and ischemic necrosis of the extremities (gangrene) is a serious problem in the diabetic population.

Nearly 99% of all infarcts result from thrombotic or embolic events, and almost all result from arterial occlusion. Occasionally, infarction may also be caused by other mechanisms, such as local vasospasm, expansion of an atheroma secondary to intraplaque hemorrhage, or extrinsic compression of a vessel (e.g., by tumor). Uncommon causes include vessel twisting (e.g., in testicular torsion or bowel volvulus), vascular compression by edema or entrapment in a hernia sac, or traumatic vessel rupture. Although venous thrombosis can cause infarction, it more often merely induces venous obstruction and congestion. Usually, bypass channels open rapidly after the occlusion forms, providing some outflow from the area that, in turn, improves the arterial inflow. Infarcts caused by venous thrombosis are more likely in organs with a single venous outflow channel (e.g., testis and ovary).

### Morphology

Infarcts are classified on the basis of their color (reflecting the amount of hemorrhage) and the presence or absence of microbial infection. Therefore, infarcts may be either red (hemorrhagic) or white (anemic) and may be either septic or bland.

**Red infarcts** (Fig. 4-18A) occur (1) with venous occlusions (such as in ovarian torsion); (2) in loose tissues (such as lung) that allow blood to collect in the infarcted zone; (3) in tissues with dual circulations such as lung and small intestine, permitting flow of blood from an unobstructed parallel supply into a necrotic area (such perfusion not being sufficient to rescue the ischemic tissues); (4) in tissues that were previously congested because of sluggish venous outflow; (5) when flow is re-established to a site of previous arterial occlusion and necrosis (e.g., fragmentation of an occlusive embolus or angioplasty of a thrombotic lesion).

**White infarcts** occur with arterial occlusions or in solid organs (such as heart, spleen, and kidney), where the solidity of the tissue limits the amount of hemorrhage that can seep into the area of ischemic necrosis from adjoining capillary beds (Fig. 4-18B).

All infarcts tend to be wedge shaped, with the occluded vessel at the apex and the periphery of the organ forming the base (see Fig. 4-18); when the base is a serosal surface there can be an overlying fibrinous exudate. At the outset, all infarcts are poorly defined and slightly hemorrhagic. The margins of both types of infarcts tend to become better defined with time by a narrow rim of congestion attributable to inflammation at the edge of the lesion.

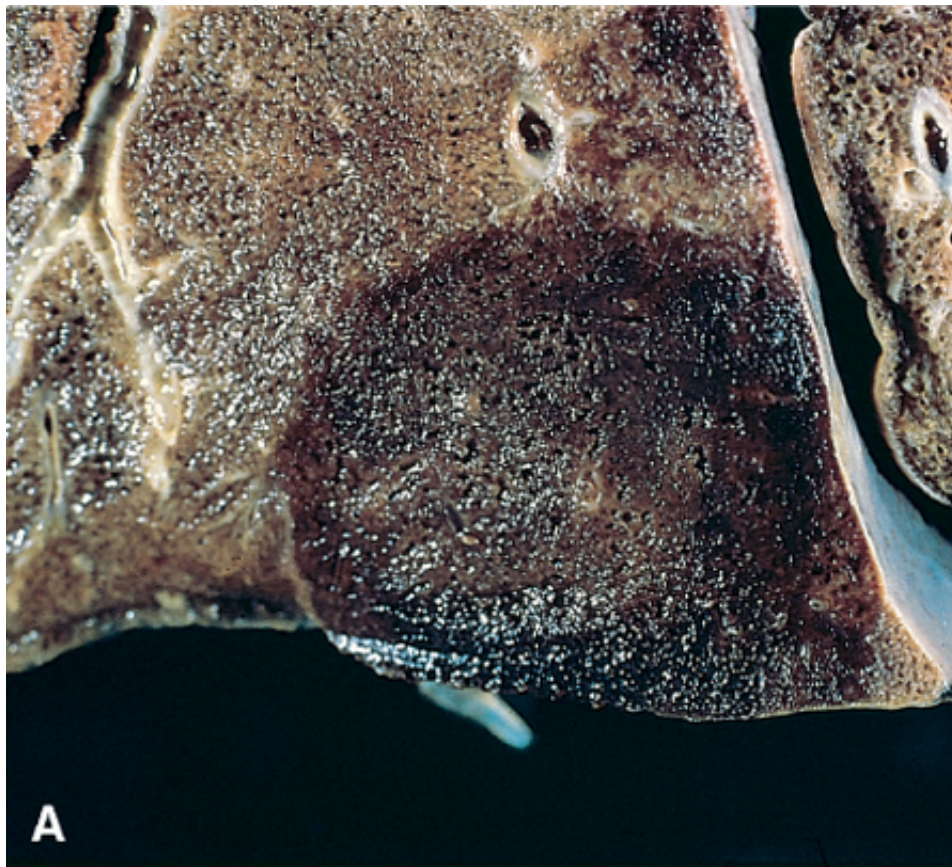
In solid organs, the relatively few extravasated red cells are lysed, with

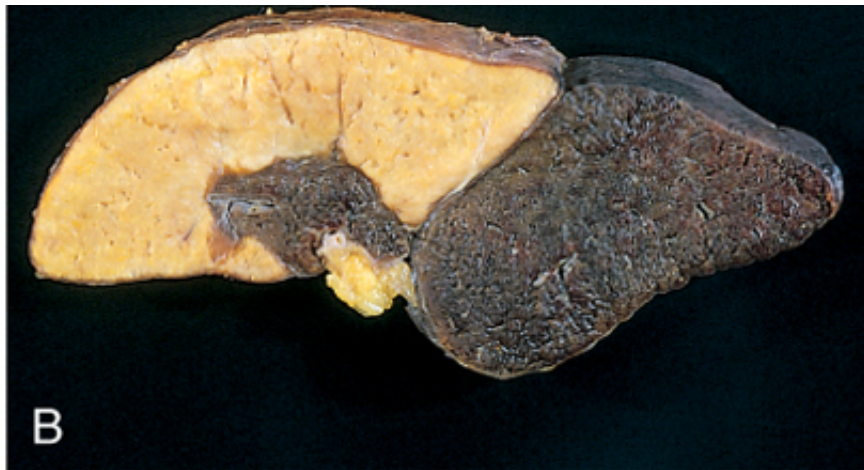


the released hemoglobin remaining in the form of hemosiderin. Thus, infarcts resulting from arterial occlusions typically become progressively more pale and sharply defined with time (see Fig. 4-18B). In spongy organs, by comparison, the hemorrhage is too extensive to permit the lesion ever to become pale (see Fig. 4-18A). Over the course of a few days, however, it does become firmer and browner, reflecting the accumulation of hemosiderin pigment.

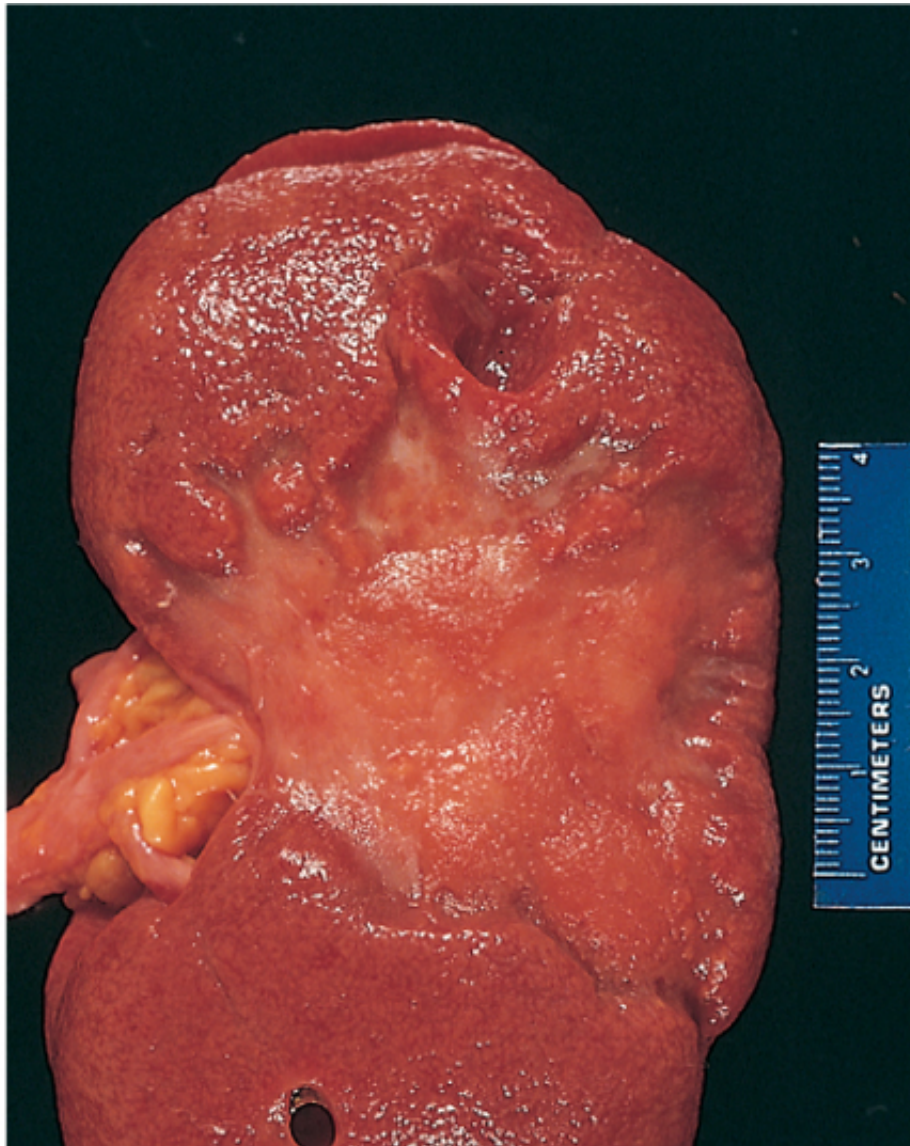
The dominant histologic characteristic of infarction is **ischemic coagulative necrosis** (Chapter 1). An inflammatory response begins to develop along the margins of infarcts within a few hours and is usually well defined within 1 to 2 days. Eventually the inflammatory response is followed by a reparative response beginning in the preserved margins (Chapter 3). In stable or labile tissues, parenchymal regeneration can occur at the periphery, where underlying stromal architecture is spared. However, most infarcts are ultimately replaced by scar (Fig. 4-19). The brain is an exception to these generalizations; ischemic tissue injury in the central nervous system results in liquefactive necrosis (Chapter 1).

**Septic infarctions** occur when bacterial vegetations from a heart valve embolize or when microbes seed an area of necrotic tissue. In these cases the infarct is converted into an abscess, with a correspondingly greater inflammatory response (Chapter 2). The eventual sequence of organization, however, follows the pattern previously described.

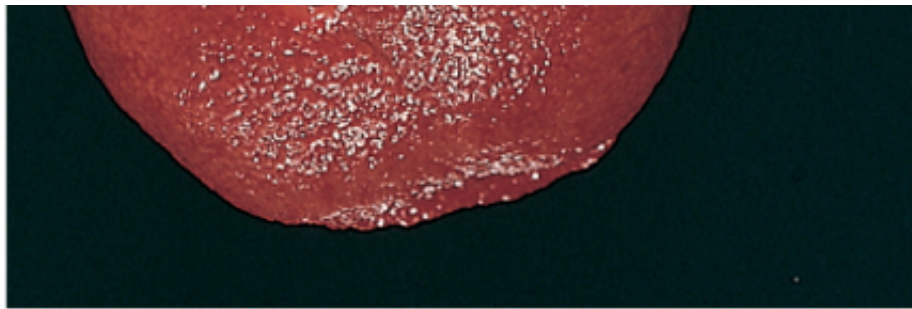




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 Figure 4-18 Red and white infarcts. **A**, Hemorrhagic, roughly wedge-shaped pulmonary infarct (*red infarct*). **B**, Sharply demarcated pale infarct in the spleen (*white infarct*).







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Figure 4-19 Remote kidney infarct, now replaced by a large fibrotic scar.

### *Factors That Influence Development of an Infarct*

Vascular occlusion can have no or minimal effect, or can cause death of a tissue or even the individual. *The major determinants of the eventual outcome include the nature of the vascular supply, the rate of development of the occlusion, vulnerability to hypoxia, and the oxygen content of blood.*

#### Nature of the Vascular Supply

The availability of an alternative blood supply is the most important determinant of whether occlusion of a vessel will cause damage. For example, as mentioned above, lungs have a dual pulmonary and bronchial artery blood supply; thus, obstruction of small pulmonary arterioles does not cause infarction in an otherwise healthy individual with an intact bronchial circulation. Similarly, the liver, with its dual hepatic artery and portal vein circulation, and the hand and forearm, with their dual radial and ulnar arterial supply, are all relatively resistant to infarction. In contrast, renal and splenic circulations are end-arterial, and obstruction of such vessels generally causes infarction.

#### Rate of Development of Occlusion

Slowly developing occlusions are less likely to cause infarction because they provide time for the development of alternative perfusion pathways. For example, small interarteriolar anastomoses—normally with minimal functional flow—interconnect the three major coronary arteries in the heart. If one of the coronaries is slowly occluded (e.g., by an encroaching atherosclerotic plaque), flow within this collateral circulation may increase sufficiently to prevent infarction, even though the major coronary artery is eventually occluded.

#### Vulnerability to Hypoxia

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The susceptibility of a tissue to hypoxia influences the likelihood of infarction. Neurons undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. Myocardial cells, though hardier than neurons, are also quite sensitive and die after only 20 to 30 minutes of ischemia. In contrast, fibroblasts within myocardium remain viable after many hours of ischemia.

#### Oxygen Content of Blood

The partial pressure of oxygen in blood also determines the outcome of vascular occlusion. Partial flow obstruction of a small vessel in an anemic or cyanotic patient might lead to tissue infarction, whereas it would be without effect under conditions of normal oxygen tension. In this way congestive heart failure, with compromised flow and ventilation, could cause infarction in the setting of an otherwise inconsequential blockage.

## **SUMMARY**

### **Infarction**

Infarcts are areas of ischemic, usually coagulative, necrosis caused by occlusion of arterial supply or less commonly venous drainage. Infarcts are most commonly caused by formation of occlusive arterial thrombi, or embolization of arterial or venous thrombi. Infarcts caused by venous occlusion, or in loose tissues with dual blood supply, are typically hemorrhagic (red) whereas those caused by arterial occlusion in compact tissues are pale (white) in color.







## SHOCK

Shock is the final common pathway for a number of potentially lethal clinical events, including severe burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis. Regardless of the cause, *shock gives rise to systemic hypoperfusion; it can be caused either by reduced cardiac output or by reduced blood volume. The end results are hypotension, impaired tissue perfusion, and cellular hypoxia.* Although the hypoperfusion initially causes only reversible cellular injury, persistence of shock eventually causes irreversible damage and culminate in the death of the patient.

There are three general categories of shock: cardiogenic, hypovolemic, and septic (Table 4-3). The first two, cardiogenic and hypovolemic shock, are fairly straightforward; septic shock is substantially more complicated and

*Cardiogenic shock* results from failure of the cardiac pump. This may be caused by myocardial infarction, arrhythmias, extrinsic compression (cardiac tamponade, Chapter 11), or outflow obstruction (pulmonary embolism). *Hypovolemic shock* results from loss of blood or plasma volume. This may be caused by severe burns, or trauma. *Septic shock* is caused by microbial infection. Most commonly this is caused by gram-negative infections (*endotoxic shock*), but it can also occur with gram-positive and fungal infections. Bacteremia can lead to septic shock; host inflammatory responses to local extravascular infection can also

Table 4-3. Three Major Types of Shock

Type of Shock	Clinical Examples	Principal Mechanisms
<b>Cardiogenic</b>	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial dysfunction or obstruction to outflow
<b>Hypovolemic</b>	Hemorrhage Fluid loss (e.g., vomiting, diarrhea, burns, or trauma)	Inadequate blood or plasma volume
<b>Septic</b>	Overwhelming microbial infections Endotoxic shock Gram-positive septicemia Fungal sepsis Superantigens (e.g. toxic shock syndrome)	Peripheral vasodilation and pooling of blood; endothelial cell damage; disseminated intravascular coagulation; activation of the complement system

Less commonly, shock may occur in the setting of an anesthetic accident or a spinal cord injury (resulting in loss of vascular tone and peripheral pooling of blood). *Anaphylactic shock* represents systemic vasodilation caused by an immunoglobulin E hypersensitivity reaction (Chapter 5). In these situations, acute systemic hypoperfusion and cellular anoxia.

### Pathogenesis of Septic Shock

With a 25% to 50% mortality rate, septic shock ranks first among the causes of death in intensive care. Approximately 200,000 deaths annually in the United States. Moreover, the continuing increase in the incidence of shock, despite improved life support for high-risk patients, an increase in invasive procedures, and the growing numbers of patients with immunodeficiency (secondary to chemotherapy, immunosuppression, or infection with the human immunodeficiency virus) suggest that the innate immune response to infectious organisms that may be blood borne or localized to a particular

Most cases of septic shock (approximately 70%) are caused by endotoxin-producing gram-negative *endotoxic shock*. Endotoxins are bacterial wall lipopolysaccharides (LPS) consisting of a toxic fatty acid chain, a core polysaccharide, and a complex polysaccharide coat (including *O antigen*) unique for each species. Gram-positive bacteria and fungi can also elicit septic shock.

All of the cellular and hemodynamic effects of septic shock can be reproduced by LPS injection alone. LPS-binding protein, and the complex then binds to a specific receptor (CD14) on monocytes, mainly CD14 (even at doses as minute as  $10 \text{ pg/mL}$ ) results in intracellular signaling via an associated protein, resulting in profound activation of mononuclear cells and production of potent effector cytokines. These cytokines act on endothelial cells and have a variety of effects including reduced synthesis of anti-thrombotic pathway inhibitor and thrombomodulin (see Fig. 4-7). The effects of the cytokines may be amplified by other cells.

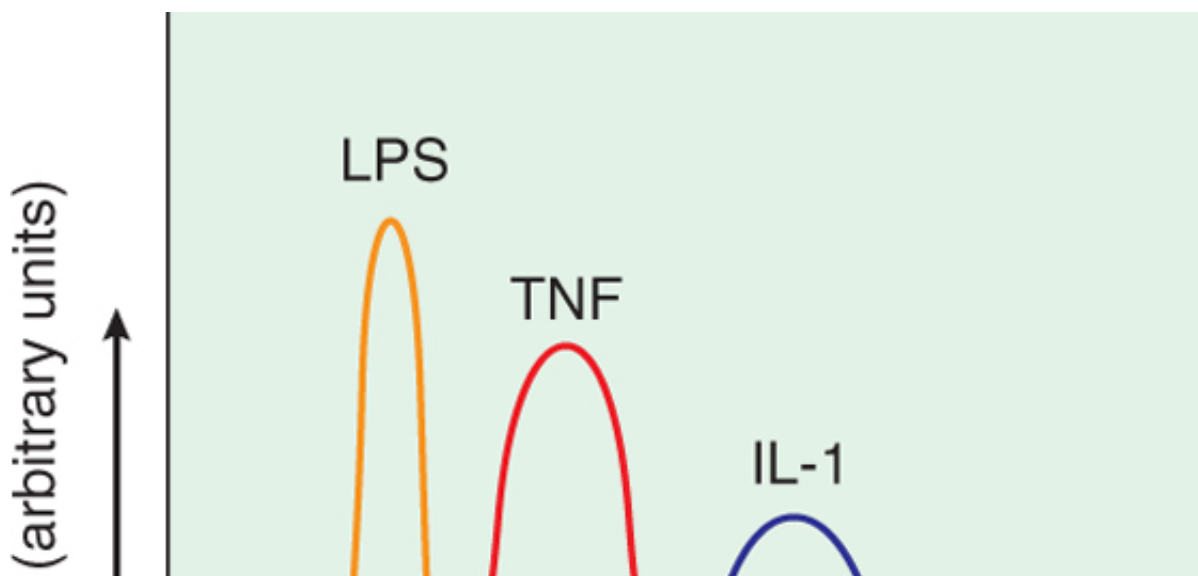
TLR-mediated activation helps to trigger the innate immune system to efficiently eradicate invading pathogens. Depending on the dosage and the extent of immune and vascular activation, the secondary effects range from beneficial to pathologic changes, including fatal shock.

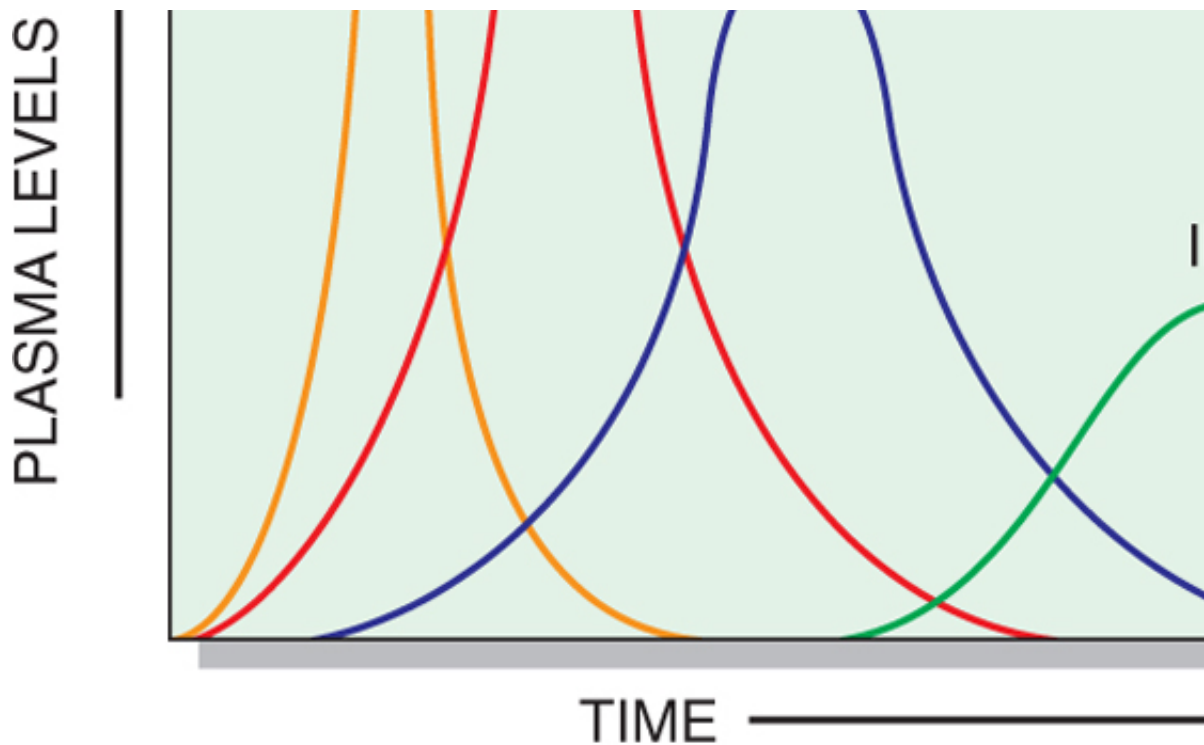
At low doses, LPS predominantly activates monocytes, macrophages, and neutrophils; it can also contribute to local eradication of bacteria. Mononuclear phagocytes respond to LPS by producing cytokines. Both TNF and IL-1 act on endothelial cells (and other cell types) to produce additional cytokines and adhesion molecules (Chapter 2). Thus, the initial release of LPS results in a circumscribed cytokine response that enhances the *local* acute inflammatory response and improves clearance of the infection.

With moderately severe infections, and therefore with higher levels of LPS (and a consequent augmented cytokine-induced secondary effectors (e.g., nitric oxide<sub>R</sub> and platelet-activating factor; Chapter 2) effects of TNF and IL-1 may begin to be seen, including fever, increased synthesis of acute-phase reactants, and circulating neutrophils (see Fig. 4-21). Higher LPS levels tip the endothelium toward a net procoagulant state.

Finally, at still higher levels of LPS, the syndrome of septic shock supervenes (see Fig. 4-21); the now at high levels, result in

Systemic vasodilation (hypotension) Diminished myocardial contractility Widespread endothelial damage and systemic leukocyte adhesion and diffuse alveolar capillary damage in the lung (Chapter 13) culminating in disseminated intravascular coagulation (DIC) (Chapter 12)





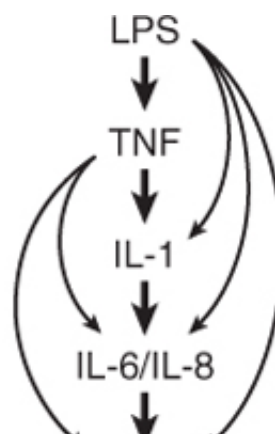
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Figure 4-20 Cytokine cascade in sepsis. After lipopolysaccharide (LPS) release there are successive waves of tumor necrosis factor (TNF) and interleukin-6 (IL-6) secretion. (Modified from Abbas AK, et al: Cellular and Molecular Immunology, 4th ed. Philadelphia: Elsevier; 2004.)

The hypoperfusion resulting from the combined effects of widespread vasodilation, myocardial pump failure, and *system failure* that affects the liver, kidneys, and central nervous system, among others. Unless the shock (or overload) is rapidly brought under control, the patient usually dies. In some experimental animal models, the use of monoclonal antibodies to neutralize the secondary mediators (e.g., nitric oxide synthase inhibitors), or pharmacologic inhibitors of the secondary mediators (e.g., nitric oxide synthase inhibitors), protecting against septic shock. Unfortunately, these interventions have not yet proved of significance because many different pathways and mediators are activated by LPS.

An interesting group of bacterial proteins called *superantigens* also causes a syndrome similar to *toxin 1*, responsible for the *toxic shock syndrome*. Superantigens are polyclonal T-lymphocyte activators that cause massive inflammatory cytokine cascades similar to those that occur in response to LPS. Their actions can have manifestations ranging from a diffuse rash to vasodilation, hypotension, and death.

### Stages of Shock







If the underlying causes are not corrected, shock passes imperceptibly to the progressive phase, hypoxia. In the setting of persistent oxygen deficit, intracellular aerobic respiration is replaced by anaerobic production of **lactic acid**. The resultant metabolic *lactic acidosis* lowers the tissue pH and blunts cellular metabolism, and blood begins to pool in the microcirculation. Peripheral pooling not only worsens the cardiac output but also increases the risk of developing anoxic injury with subsequent DIC. With widespread tissue hypoxia, vital organs begin to fail.

Unless there is intervention, the process eventually enters an irreversible stage. Widespread cell membrane leakage, further aggravating the shock state. Myocardial contractile function worsens, in part because of myocardial depression. If the bowel allows intestinal flora to enter the circulation, endotoxic shock may also be superimposed. A renal shutdown due to ischemic acute tubular necrosis ([Chapter 14](#)), and, despite heroic measures, the process inevitably culminates in death.

### Morphology

The cellular and tissue changes induced by shock are essentially those of hypoxic-ischemic injury, a combination of hypoperfusion and microvascular thrombosis. Since shock is **of many organ systems**, the cellular changes may appear in any tissue. Nevertheless, the most evident in the brain, heart, kidneys, adrenal glands, and gastrointestinal tract. Fibrin deposition is evident in virtually any tissue, although they are usually most readily visualized in kidney glomeruli. The **changes** in shock are those seen in all forms of stress; essentially there is cortical atrophy, which reflects not adrenal exhaustion but instead conversion of the relatively inactive vacuolated cells to metabolically active cells that use stored lipids for the synthesis of steroids. The kidneys show acute tubular necrosis ([Chapter 14](#)) so that oliguria, anuria, and electrolyte disturbances develop. The **gastrointestinal tract** may manifest focal mucosal hemorrhage and necrosis, but is seldom affected in pure hypovolemic shock, because they are somewhat resistant to ischemia. However, when shock is caused by bacterial sepsis or trauma, changes of **diffuse alveolar damage** ([Chapter 13](#)) may develop, the so-called shock lung.

With the exception of neuronal and myocyte ischemic loss, virtually all tissues may recover if the patient survives. Unfortunately, most patients with irreversible changes due to severe shock die, and few tissues can recover.

### Clinical Course

The clinical manifestations of shock depend on the precipitating insult. In hypovolemic and cardiogenic shock, there is *hypotension*; a weak, rapid pulse; tachypnea; and cool, clammy, cyanotic skin. In septic shock, there is hyperemia and flushed skin as a result of peripheral vasodilation. The initial threat to life stems from the underlying cause (e.g., a myocardial infarct, severe hemorrhage, or bacterial infection). Rapidly, however, the cardiovascular changes that occur secondary to the shock state materially worsen the problem. If patients survive the initial course, they may be dominated by renal insufficiency and marked by a progressive fall in urine output as well as acid-base imbalances.

The prognosis varies with the origin of shock and its duration. Thus, 80% to 90% of young, otherwise healthy patients with shock survive with appropriate management, whereas cardiogenic shock associated with extensive myocardial infarction carries a mortality rate of 75%, even with care that is state of the art.

## SUMMARY

### Shock

Shock causes systemic hypoperfusion due to either reduced cardiac output or decreased blood volume. The most common causes of shock are cardiogenic (cardiac output reduced, for example, to myocardial infarction), hypovolemic (due, for example, to blood loss or dehydration), and septic (due to blood-borne infections). Septic shock results from the host innate immune response to bacterial toxins and molecules (most commonly endotoxin), with systemic production of cytokines that affect endothelial and inflammatory cell activation. Hypotension, DIC, and organ failure constitute the clinical triad of septic shock. Shock of any form causes pathological tissue hypoxic injury.

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*mechanisms of thrombus formation with emphasis on targets for therapeutic intervention.]*



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## 5 Diseases of the Immune System

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*Immunity* refers to protection against infections, and the immune system is the collection of cells and molecules that are responsible for defending us against the countless pathogenic microbes in our environment. Deficiencies in immune defenses result in an increased susceptibility to infections, which can be life-threatening if the deficits are not corrected. On the other hand, the immune system is itself capable of causing great harm and is the root cause of some of the most vexing and intractable diseases of the modern world. Thus, diseases of immunity range from those caused by "too little" to those caused by "too much or inappropriate" immune activity. This chapter starts with a brief review of some of the basic concepts of lymphocyte biology and normal immune responses, which establishes the foundation for our discussion of transplant rejection and diseases caused by defective or inappropriate immune responses. The chapter concludes with a discussion of *amyloidosis*, a disease characterized by the abnormal extracellular deposition of certain proteins (some of which are produced in the setting of immune responses).



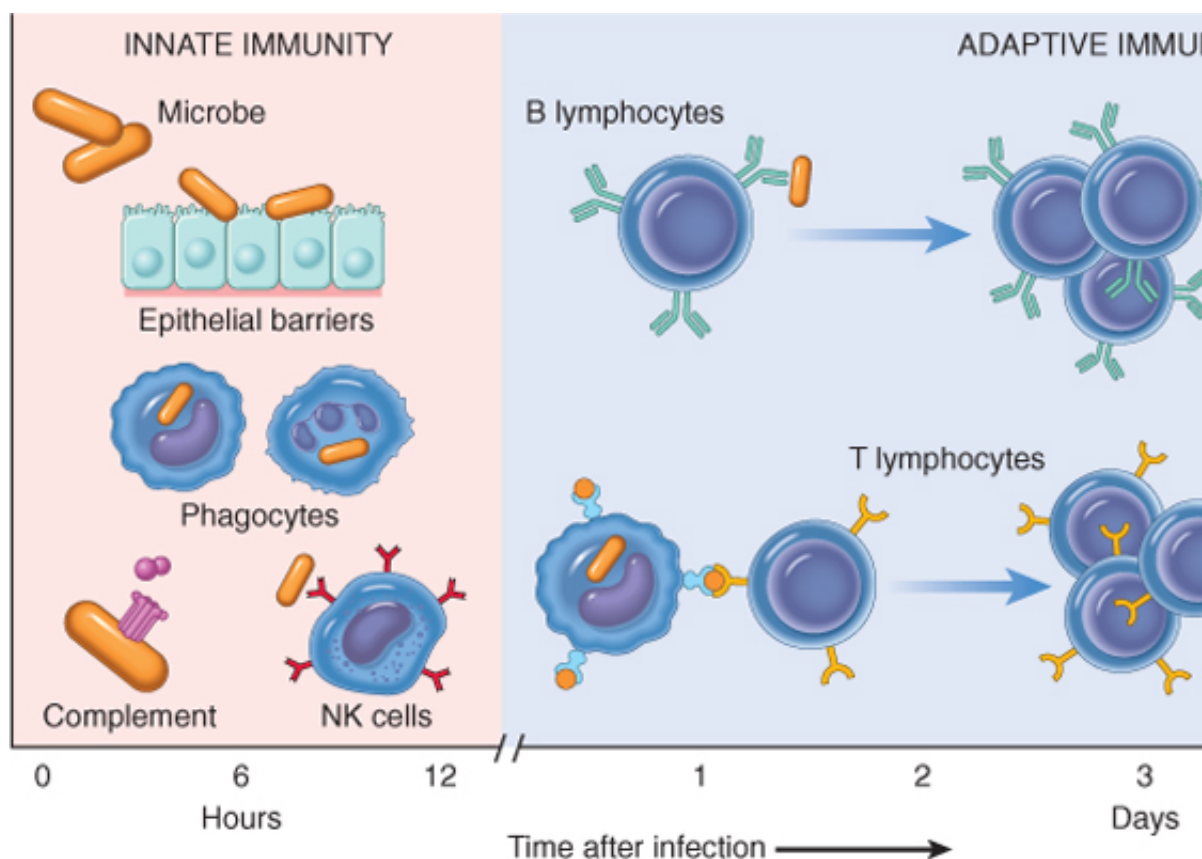
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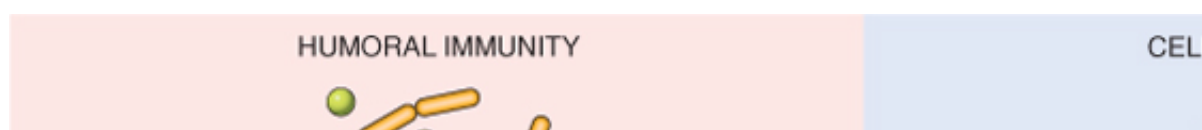
## INNATE AND ADAPTIVE IMMUNITY

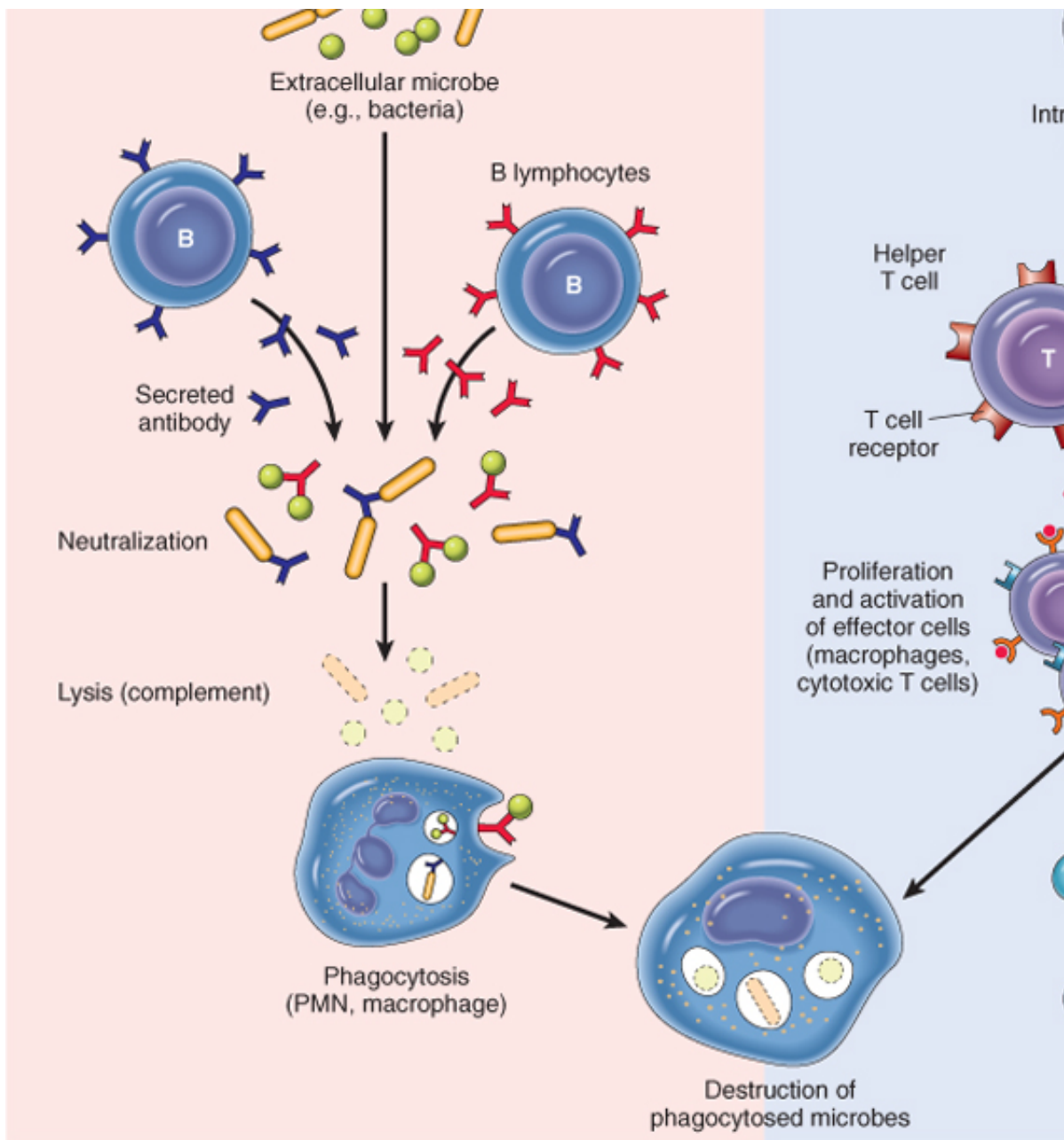


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Figure 5-1 The principal mechanisms of innate immunity and adaptive immunity. NK ce

Defense against microbes consists of two types of reactions (Fig. 5-1). *Innate immunity* (also called *innate immunity*) is mediated by cells and proteins that are always present and poised to fight against microbes and a response to infection. The major components of innate immunity are epithelial barriers of the skin, tract, which prevent microbe entry (and have to be breached for a microbe to establish infection); macrophages; a specialized cell type called the natural killer (NK) cell; and several circulating proteins which are the proteins of the complement system.

The innate immune response is able to prevent and control many infections. However, many pathogens overcome innate immune defenses, and protection against these infections requires the more powerful (also called acquired, or specific, immunity). Adaptive immunity is normally silent and responds to microbes by becoming active, expanding, and generating potent mechanisms for neutralizing and destroying them. The components of the adaptive immune system are lymphocytes and their products. By convention, the "cell-mediated" response refers to adaptive immunity.





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 Figure 5-2 Humoral and cell-mediated immunity. In humoral immunity, B lymphocytes secrete antibodies that eli  
 immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected ce

There are two types of adaptive immune responses: *humoral immunity*, mediated by soluble antib lymphocytes (also called B cells), and *cell-mediated (or cellular) immunity*, mediated by T lympho Antibodies provide protection against extracellular microbes in the blood, mucosal secretions, and defense against intracellular microbes. They work by either directly killing infected cells (accompli activating phagocytes to kill ingested microbes, via the production of soluble protein mediators cal The main properties and functions of the cells of the immune system are described below.

When the immune system is inappropriately triggered or not properly controlled, the same mecha cause tissue injury and disease. The reaction of the cells of innate and adaptive immunity may be discussed in [Chapter 2](#), inflammation is a beneficial process, but it is also the basis of many huma discuss the ways by which the immune response triggers pathologic inflammatory reactions.



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## CELLS AND TISSUES OF THE IMMUNE SYSTEM

The cells of the immune system consist of lymphocytes, which are the mediators of adaptive immunity (APCs), which capture and display microbial and other antigens to the lymphocytes; and various effector cells that eliminate the antigens (typically, microbes), the ultimate "effect" of the immune response. A remarkable feature is how intricately and efficiently the responses of these different cell types are orchestrated and regulated.

### Lymphocytes

Lymphocytes are present in the circulation and in various lymphoid organs. Although all lymphocytes there are actually several functionally and phenotypically distinct lymphocyte populations. Lymphocytes are generated in primary lymphoid organs; T lymphocytes are so called because they mature in the thymus, while B lymphocytes mature in the bone marrow. Each T or B lymphocyte expresses receptors for a single antigen, and the total population (in humans) is capable of recognizing tens or hundreds of millions of antigens. This enormous diversity is achieved by the somatic rearrangement of antigen receptor genes during lymphocyte maturation, and variable joining of different gene segments to form antigen receptors. These antigen receptors are rearranged in not in any other cell. Therefore, the *demonstration of antigen receptor gene rearrangements by molecular cloning, or PCR) is a definitive marker of T or B lymphocytes*. Such analyses are used in classification (Fig. 12). Furthermore, because each lymphocyte has a unique DNA rearrangement (and hence a unique DNA fingerprint), *the rearrangement in a cell population can be used to distinguish polyclonal (non-neoplastic) lymphocytes from monoclonal (neoplastic) expansions*.

### T Lymphocytes

Thymus-derived, or T, lymphocytes are the effector cells of cellular immunity and provide important functions. T cells constitute 60% to 70% of the lymphocytes in peripheral blood and are the major cells in the periarteriolar sheaths and lymph node interfollicular zones. T cells do not detect free or circulating antigens; rather, (>95%) of T cells recognize only peptide fragments of protein antigens that are displayed on other cells by the major histocompatibility complex (MHC; or in humans, human leukocyte antigen [HLA] complex). The MHC is a set of genes that encode proteins that display peptides for recognition by T lymphocytes. By forcing T cells to see MHC-bound peptides, T cells can recognize antigens in other cells and thus perform their function of killing infected cells or activating macrophages to ingest protein antigens. In every individual, T cells recognize only peptides displayed by that individual's MHC molecules; in other words, are the only MHC molecules that the T cells will encounter normally. This phenomenon is called MHC restriction. In T cells, the T-cell receptor (TCR) is a heterodimer composed of disulfide-linked  $\alpha$  and  $\beta$  protein chains. The TCR has a variable region that participates in binding a particular peptide antigen and a constant region that interacts with the MHC molecules. MHC molecules are described below.

TCRs are noncovalently linked to a cluster of five invariant polypeptide chains, the  $\gamma$ ,  $\delta$ , and  $\epsilon$  proteins and two  $\zeta$  chains (see Fig. 5-3A). The CD3 proteins and  $\zeta$  chains do not themselves bind antigens; instead, they interact with the TCR to transduce intracellular signals after TCR recognition of antigen. In addition to the TCR, a number of other invariant function-associated molecules, CD4 and CD8 are expressed on distinct T-cell subsets as coreceptors for T-cell activation. During antigen recognition, CD4 molecules on T cells bind to invariant class II MHC molecules (see later) on selected APCs; in an analogous fashion, CD8 binds to class I MHC molecules. CD4 is expressed on all mature T cells, whereas CD8 is expressed on about 30% of T cells; in normal healthy individuals, CD4<sup>+</sup> and CD8<sup>+</sup> T cells (called CD4<sup>+</sup> and CD8<sup>+</sup> cells, respectively) perform different functions. CD4<sup>+</sup> T cells are called "helper" T cells because they secrete soluble molecules (*cytokines*) that help B cells to produce antibodies and also help macrophages to destroy phagocytosed microbes. The central role of CD4<sup>+</sup> helper T cells is the severe compromise that results from the destruction of this subset by human immunodeficiency virus (HIV). CD8<sup>+</sup> T cells also secrete cytokines, but they play a more important role in directly killing virus-infected or tumor cells (CTLs). Other important invariant proteins on T cells include CD28, which functions as a costimulator induced on APCs by microbes (and are called costimulators), and various adhesion molecules that

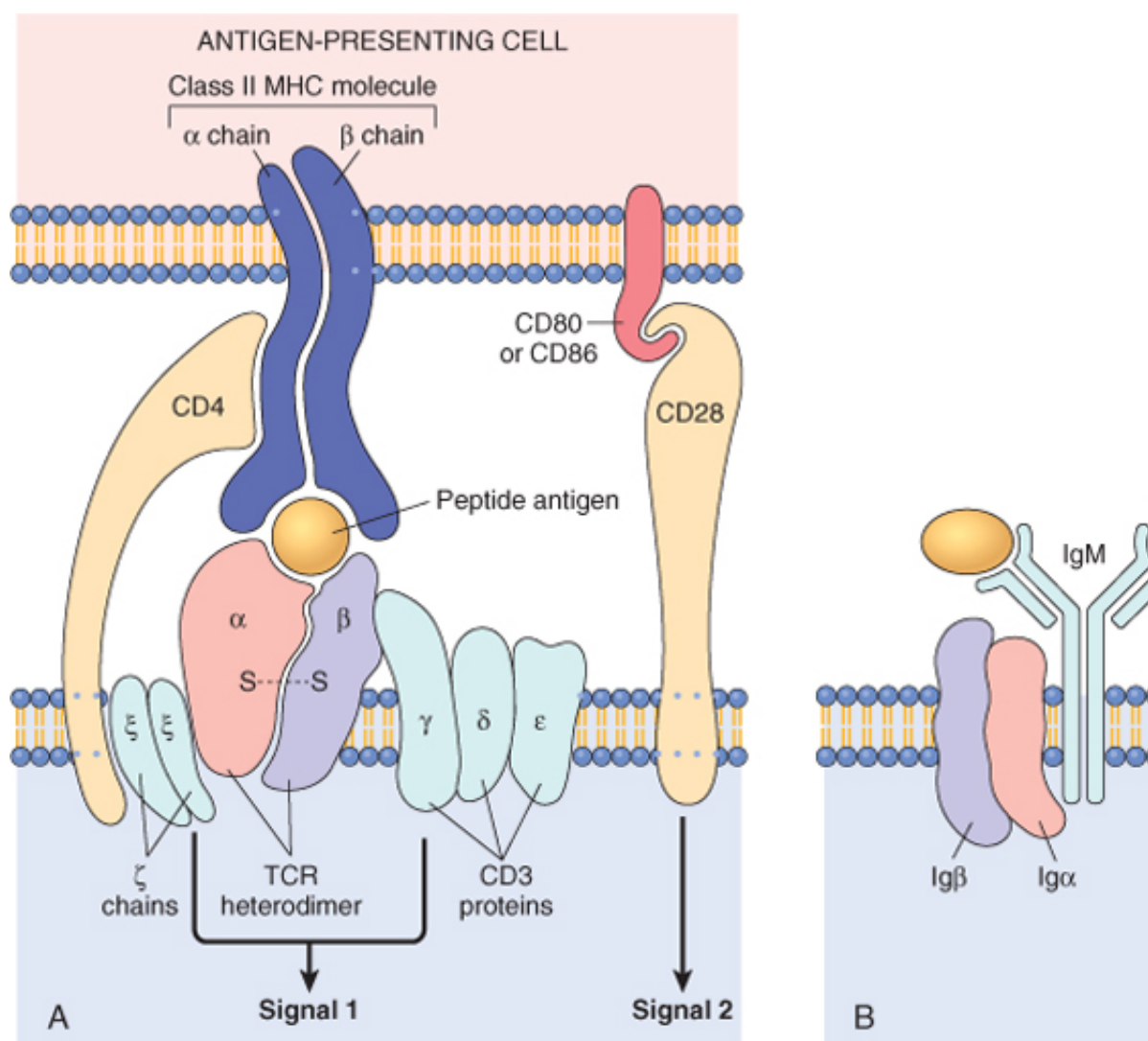


cells and APCs and control the migration of the T cells to different tissues.

In a minority of peripheral blood T cells and in many of the T cells associated with mucosal surface the TCRs are heterodimers of  $\gamma$  and  $\delta$  chains, which are similar but not identical to the  $\alpha$  and  $\beta$  chains. These T cells do not express CD4 or CD8 and recognize nonprotein molecules (e.g., bacterial lipoglycans), but the importance of these T cells in host defense is also not established. Another small population of T cells expresses markers of T cells and NK cells. These *NKT cells* recognize lipid antigens presented by a non-MHC molecule. The antigen receptors of  $\gamma\delta$  T cells and NKT cells are distinct from the antigen receptors of "conventional" T cells, suggesting that the former recognize conserved microbial structures. These cells resemble cells of innate immunity.

Another population of T cells that is receiving great attention is called *regulatory T lymphocytes*. T cells that suppress the response of other T cells to self antigens, thus promoting tolerance of self antigens.

### **MHC Molecules: the Peptide Display System of Adaptive Immunity**

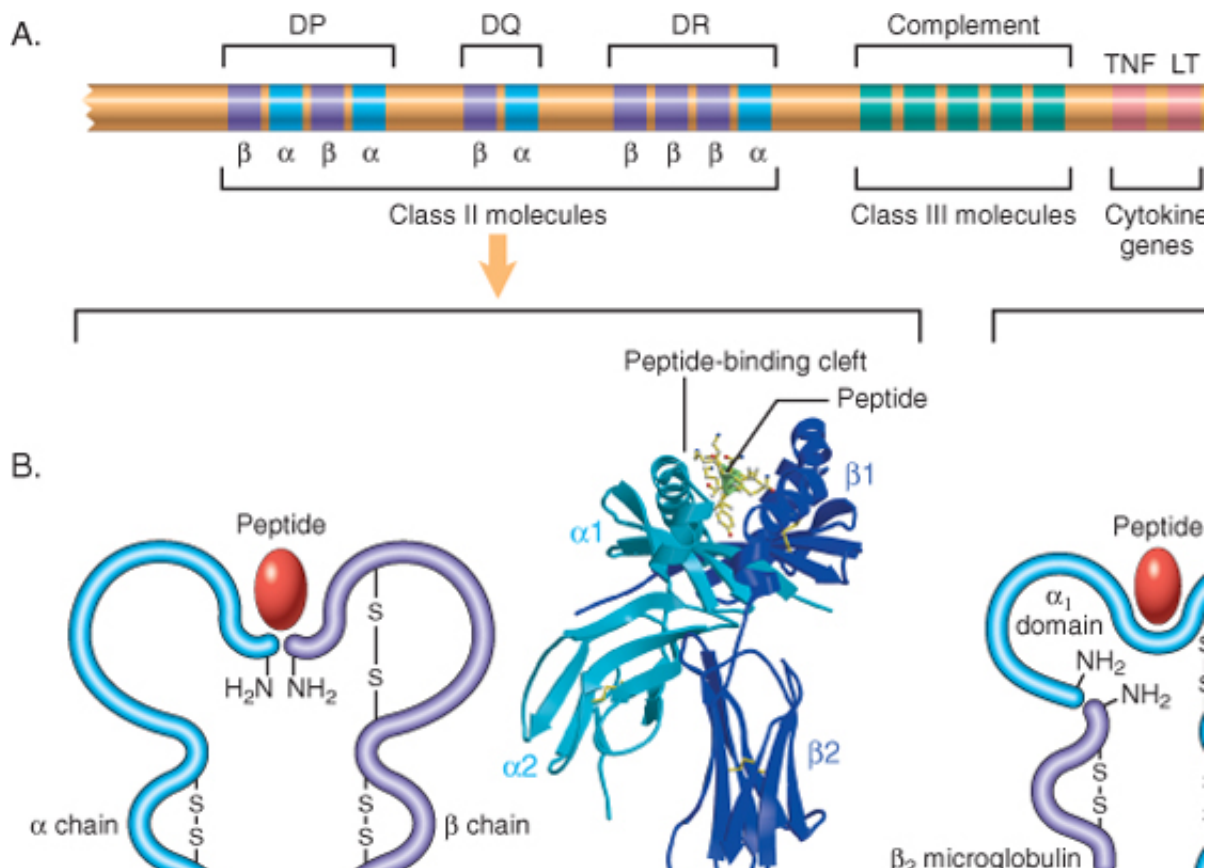


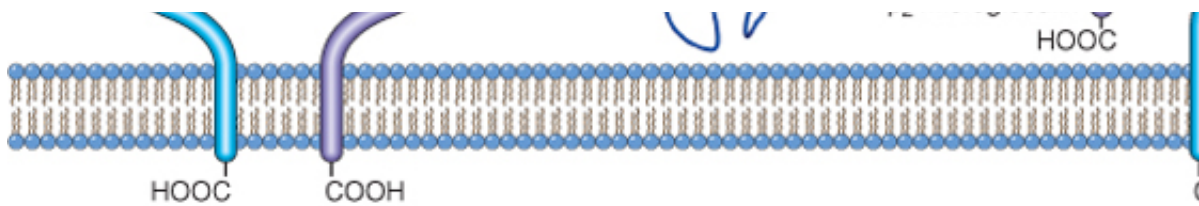
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Figure 5-3 Lymphocyte antigen receptors. **A**, The T-cell receptor (TCR) complex and other molecules involved in recognizing antigen (in the form of peptide-MHC complexes expressed on antigen-presenting cells), and the linked CD4 and CD80 or CD86 molecules are also involved in T-cell activation. (Note that some T cells express CD8 and not CD4; these molecules are also involved in T-cell activation.) The T-cell receptor complex is composed of membrane IgM (or IgD, not shown) and the associated signaling proteins Ig $\alpha$  and Ig $\beta$ . CD40L promotes B-cell activation.

Because MHC molecules are fundamental to T-cell recognition of antigens, and variations in MHC immunologic diseases, it is important to review the structure and function of these molecules. The *leukocyte antigen (HLA) complex*, consists of a cluster of genes on chromosome 6 (Fig. 5-4). The is, there are several alternative forms (*alleles*) of a gene at each locus (e.g., >400 different HLA-B diversity provides a system whereby a vast array of peptides can be displayed by MHC molecules see, this polymorphism also constitutes a formidable barrier to organ transplantation.

On the basis of their chemical structure, tissue distribution, and function, MHC gene products fall i

*Class I MHC molecules* are encoded by three closely linked loci, designated *HLA-A*, *HLA-B*, and *HLA-C*. These molecules are a heterodimer, consisting of a polymorphic 44-kD  $\alpha$  chain noncovalently associated with  $\beta_2$ -microglobulin (encoded by a separate gene on chromosome 15). The extracellular portion of these molecules binds foreign peptides for presentation to CD8<sup>+</sup> T cells. In general, class I molecules are derived from proteins synthesized within the cell (e.g., viral antigens). Because class I MHC molecules are found on all nucleated cells, all virus-infected cells can be detected and eliminated by CTLs. *Class II MHC molecules* are encoded by two closely linked loci, designated *HLA-D* and *HLA-DQ*. The *HLA-D* region, which contains at least three subregions: *DP*, *DQ*, and *DR*. Class II MHC molecules consist of linked polymorphic  $\alpha$  and  $\beta$  subunits (see Fig. 5-4). As in class I, the extracellular portion of these molecules has a cleft for the binding of antigenic peptides. Unlike in class I, the tissue distribution of class II molecules is restricted; they are constitutively expressed mainly on APCs (notably, dendritic cells), and macrophages. Class II molecules bind to peptides derived from proteins synthesized outside the cell (e.g., those from extracellular pathogens). This allows CD4<sup>+</sup> T cells to recognize the presence of extracellular pathogens and to orchestrate an immune response. Some of the complement components (C2, C3, and Bf); genes encoding tumor necrosis factor (TNF- $\beta$ ) are also located within the MHC. Although genetically linked to class I and II molecules, cytokine genes do not form a part of the peptide display system and will not be discussed further.





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Figure 5-4 The HLA complex and the structure of HLA molecules. **A**, The location of genes in the HLA complex. The class II region also contains genes that encode several proteins involved in antigen processing (not shown). **B**, The structure of class I and class II HLA molecules. LT, leukotriene; TNF, tumor necrosis factor. (Crystal structures are from the Laboratory of Molecular Biology, National Institutes of Health, Bethesda, Maryland.)

Every individual inherits one HLA allele from each parent and thus typically expresses two different HLA molecules. A heterozygous individual can therefore express six different class I HLA molecules: three of maternal origin and three of paternal origin. Similarly, a given individual expresses maternal and paternal alleles of the class II MHC loci; because each class II-expressing cell can have as many as 20 different class II HLA molecules, each cell can bind to different peptide fragments depending on the particular amino acid sequence of a given peptide. This ability of MHC molecules allows each cell to present a wide array of peptide antigens.

As a result of the polymorphism at the major HLA loci in the population, a virtually infinite number of different HLA molecules are expressed. Each individual expresses a unique MHC antigenic profile on his or her cells. The combination of I and II HLA molecules is called the *HLA haplotype*. The implications of HLA polymorphism are obvious in the context of transplantation. Alleles that differ to some extent from every other individual, grafts from any person will evoke immune responses and be rejected (except, of course, for identical twins). In fact, HLA molecules were discovered in the context of transplantation. HLA molecules of the graft evoke both humoral and cell-mediated responses, even in the absence of any foreign antigens (discussed later in this chapter). This ability of MHC molecules to trigger immune responses is the basis for the "antigenic" nature of the MHC. It is believed that the polymorphism of MHC genes arose to enable the population to deal with a wide variety of microbial peptides.

The role of the MHC in T-cell stimulation also has important implications for the genetic control of immune responses. The ability of a given MHC allele to bind the peptide antigens generated from a particular pathogen will determine whether the immune system actually "sees" and responds to that pathogen. In other words, an individual will recognize and mount an immune response to an antigen only if he or she inherits MHC molecules that can bind the antigenic peptide and present it. The genetic control of MHC alleles influences both protective and harmful immune responses. For example, if the antigen is responsible for an allergic reaction, inheritance of some HLA genes may make individuals susceptible to this disease. Conversely, inheritance of certain HLA alleles, which confer responsiveness to a viral antigen, may be beneficial.

Finally, many diseases are associated with particular HLA alleles. These HLA-linked diseases can be divided into two categories: (1) *inflammatory diseases*, including ankylosing spondylitis and several postinfectious diseases associated with *HLA-B27*; and (2) *autoimmune diseases*, including autoimmune endocrinopathies, associated with certain HLA alleles. The underlying mechanisms of all these associations are not understood at present. The best known association is between the *HLA-B27* allele; individuals who possess this allele have a 90-fold greater chance (relative risk) of developing ankylosing spondylitis than those who are negative for *HLA-B27*. We will return to a discussion of HLA linkage when we consider autoimmune diseases.

## B Lymphocytes

Bone marrow-derived, or B, lymphocytes comprise 10% to 20% of the circulating peripheral lymphocytes. They are found in bone marrow and in the follicles of peripheral lymphoid tissues (lymph nodes, spleen, tonsils, and appendix). The differentiation of follicular B cells leads to the formation of a central zone of large, activated B cells in follicles, called the germinal center. The germinal center is the site of B-cell proliferation and differentiation into a cell lineage that synthesizes antibodies, also called immunoglobulins (Ig).

B cells recognize antigen via monomeric membrane-bound antibody of the immunoglobulin M (IgM) class. The B-cell receptor (BCR) complex (see Fig. 5-3B) is formed by the association of IgM molecules with the B-cell membrane. Whereas T cells can recognize and respond to many more chemical structures, including proteins, lipids, and polysaccharides; furthermore, B cells (and antibodies) recognize native (conformational) forms of these antigens. Each B cell has a unique antigen specificity. The diversity of antibodies is generated during somatic rearrangement of immunoglobulin genes.

has a unique antigen specificity. The diversity of antibodies is generated during somatic rearrangement of several invariant molecules that are responsible for signal transduction and for activation of the cell. These include the CD40 receptor, which binds to its ligand expressed on helper T cells, and CD21 (also known as CR2), which recognizes a complement breakdown product that is frequently deposited on microbes.

After stimulation, B cells differentiate into *plasma cells*, which secrete large amounts of antibodies. There are five classes, or isotypes, of immunoglobulins: IgG, IgM, and IgA constitute more than 90% of the major isotype in mucosal secretions, IgE is present in the circulation at very low concentrations and is associated with tissue mast cells, and IgD is expressed on the surfaces of B cells but is not secreted. As outlined above, antibodies have abilities to activate complement or recruit inflammatory cells and thus play a different role in host defense.

### **Natural Killer Cells**

Natural killer (NK) cells are lymphocytes that arise from the common lymphoid progenitor that give rise to T and B cells. NK cells are cells of innate immunity and do not express highly variable and clonally distributed receptors. They do not have specificities as diverse as do T cells or B cells. NK cells use a limited set of activating receptors to recognize stressed or infected cells or cells with DNA damage, and then kill these cells, thus eliminating potential reservoirs of infection. NK cells have another unique specificity. To avoid attacking normal host cells, they express inhibitory receptors that recognize self class I MHC molecules, which are expressed on all healthy cells; engagement of these receptors overrides the activating receptors and thus prevents activation of the NK cells. Infections (especially viral infections) are associated with loss of expression of class I MHC molecules. When this happens, the NK cells are able to respond to the activating ligands that were induced by the stress and ultimately destroy the infected cells.

### **Antigen-Presenting Cells**

The immune system contains several cell types that are specialized to capture microbial antigens and present them to T cells. Foremost among these APCs are dendritic cells (DCs), the major cells for displaying protein antigens to T cells and initiating immune responses. Several other cell types present antigens to different lymphocytes at various stages of the immune response.

#### **Dendritic Cells**

Cells with dendritic morphology (i.e., with fine dendritic cytoplasmic processes) occur as two functional types. More simply, DCs, are nonphagocytic cells that express high levels of class II MHC and T-cell receptors. They reside in epithelia, where they are strategically located to capture entering microbes; an example is the skin. Mature DCs are present in the T-cell zones of lymphoid tissues, where they present antigens to T cells. DCs are also present in the interstitium of many nonlymphoid organs, such as the heart and lungs, where they capture microbes that have invaded the tissues.

The second type of DCs is called *follicular dendritic cells (FDCs)*. They are located in the germinal centers of the spleen and lymph nodes. These cells bear receptors for the Fc tails of IgG and for complement proteins that bind to antibodies and complement. These cells display antigens to activated B lymphocytes in the context of class II MHC molecules, initiating antibody responses.

#### **Other APCs**

Macrophages ingest microbes and other particulate antigens and display peptides for recognition by T cells. To activate the macrophages to kill the microbes, the central reaction of cell-mediated immunity, B cells must first receive signals that stimulate antibody responses to protein antigens.

### **Effector Cells**

Many different types of leukocytes perform the ultimate task of the adaptive immune response, which is to kill or remove the pathogen. The frontline effector cells because of their ability to rapidly react against "stressed" cells. Antibody-secreting B cells and T lymphocytes, both CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> CTLs, are effector cells of humoral immunity. T lymphocytes often function in host defense together with other cells. Macrophages, which were described above, are coated with antibodies or complement, and phagocytose and destroy these microbes, thus serving as effector cells of cellular immunity. Macrophages also respond to signals from helper T cells and improve their ability to destroy microbes. T lymphocytes secrete cytokines that recruit and activate neutrophils and eosinophils, and all these cell types function in defense against various pathogens.



macrophages and eosinophils, and all these cell types function in defense against various pathogens for tissue injury in inflammatory diseases caused by abnormal immune responses.

## Lymphoid Tissues

The lymphoid tissues of the body are divided into generative (primary) organs, where lymphocytes are produced, and peripheral (secondary) lymphoid organs, where adaptive immune responses develop. The bone marrow, and the peripheral organs are the lymph nodes, spleen, and mucosal and cutaneous lymphoid tissues. Lymphocytes recirculate through the peripheral organs, searching for microbial antigens to which they can respond. A characteristic of these organs is that T and B lymphocytes are anatomically segregated until they encounter antigens. This process is described below.

### SUMMARY

#### Cells and Tissues of the Immune System

Lymphocytes are the mediators of adaptive immunity and the only cells that express diverse receptors for antigens. *T (thymus-derived) lymphocytes* express antigen receptors (TCRs) that recognize peptide fragments of protein antigens that are presented by MHC molecules on the surface of antigen-presenting cells. *B (bone marrow-derived) lymphocytes* produce membrane-bound antibodies that recognize a wide variety of antigens. B cells can become plasma cells, which secrete antibodies. *Natural killer (NK) cells* kill certain types of cells, such as some microbes, or are stressed and damaged beyond repair. NK cells express receptors that recognize MHC molecules that are normally expressed on healthy cells and can prevent them from killing normal cells. *Antigen-presenting cells (APCs)* capture microbes and other antigens and transport them to lymphoid organs, and display them for recognition by lymphocytes. The most efficient APCs are *dendritic cells*, which live in epithelia and most tissues. The lymphoid organs of the immune system are organized in tissues, some of which are the sites of production of lymphocytes (the generative lymphoid organs, the bone marrow and thymus), and others are sites where immune responses develop (the peripheral lymphoid organs, including lymph nodes, spleen, and mucosal and cutaneous lymphoid tissues).





## OVERVIEW OF NORMAL IMMUNE RESPONSES

Now that we have described the major components of the immune system, it is useful to summarize responses. This will serve as the foundation for the subsequent discussion of diseases caused by responses.

### The Early Innate Immune Response to Microbes

The principal barriers between hosts and their environment are the epithelia of the skin and the gastrointestinal tract. Infectious microbes usually enter through these routes and attempt to colonize the hosts. Epithelia act as barriers to infections, simultaneously impeding the entry of microbes and interfering with their growth through various mechanisms. If microbes are able to traverse these epithelia, they encounter the defense mechanisms of the innate immune system, which react rapidly against microbes and their products. Phagocytes, including neutrophils and macrophages, destroy them by producing microbicidal substances in these vesicles; macrophages also secrete various cytokines and lymphocyte responses. Phagocytes, dendritic cells, and many other cell types also turn on a variety of defense mechanisms, including secreted proteins called cytokines (described later), in response to recognition of microbial components; foremost among these are proteins called *Toll-like receptors*, so named because of their similarity to receptors that recognize bacterial and viral components. NK cells kill virus-infected cells and produce the cytokines. Many plasma proteins are involved in host defense, including the proteins of the complement system and the "alternative" pathway and whose products kill microbes and coat (opsonize) them for phagocytosis. Innate immune responses stimulate subsequent adaptive immunity, providing signals that are essential for the activation of antigen-specific T and B lymphocytes.

### The Capture and Display of Microbial Antigens

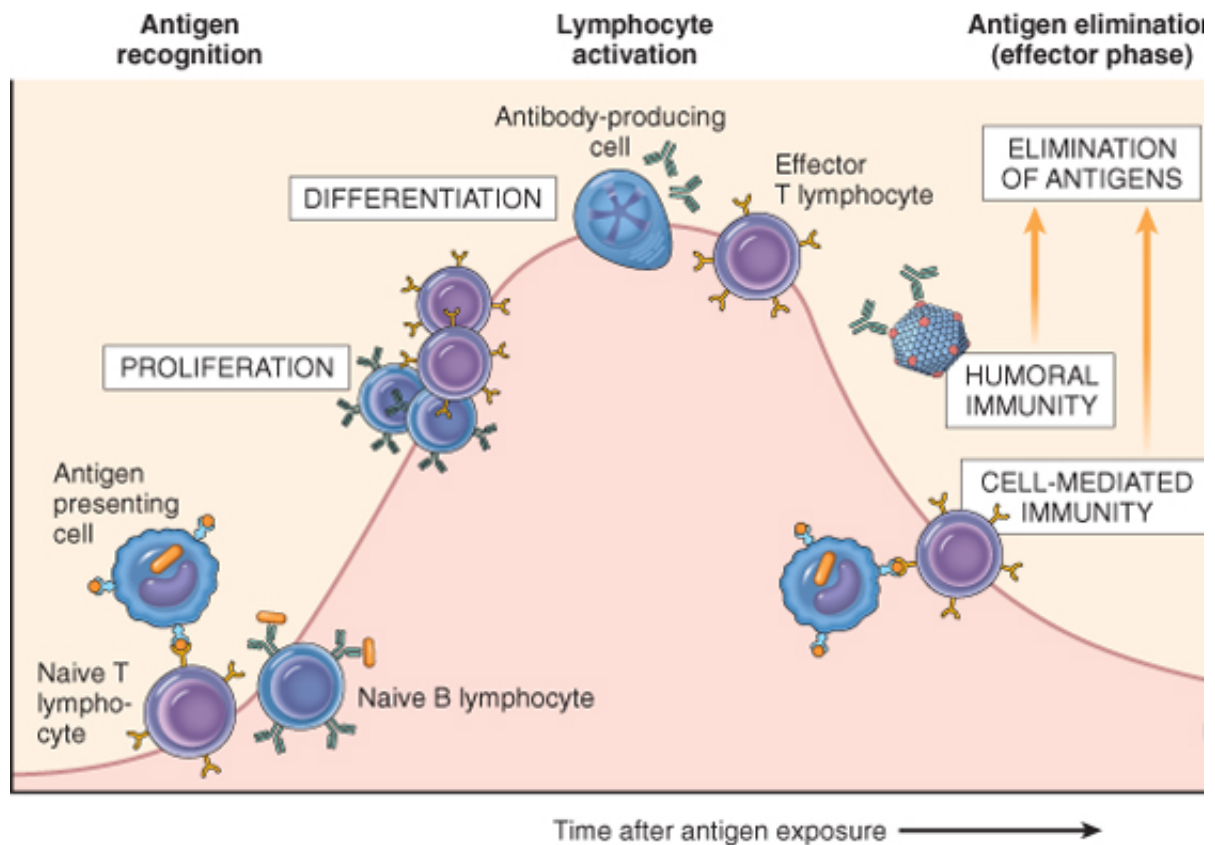
Microbes that enter through epithelia, and their protein antigens, are captured by DCs that are resident in the tissue. Bound antigens are transported to draining lymph nodes (see Fig. 5-6). Protein antigens are processed in the cytoplasm and are displayed on the surface of the APCs bound to MHC molecules. Antigens in different cellular compartments are processed by different MHC molecules and are recognized by different subsets of T cells. Antigens that are ingested by phagocytes are processed in endosomal and lysosomal vesicles, and displayed bound to class II MHC molecules. CD4<sup>+</sup> helper T cells recognize class II-associated peptides, which are usually derived from extracellular antigens. Antigens in the cytoplasm are displayed by class I MHC molecules and are recognized by CD8<sup>+</sup> cytotoxic T cells. This segregation of different antigens is key to the specialized functions of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Two classes of T cells are designed to combat microbes that are located in different cellular compartments. Polysaccharides and other nonprotein antigens, are also recognized by B lymphocytes in the lymph nodes.

At the same time as the antigens of a microbe are recognized by B and T lymphocytes, the microbe itself is also recognized by the innate immune system. In the case of immunization with a protein antigen, this innate response is induced by the adjuvant. The innate immune response activates APCs to express costimulatory molecules and secrete cytokines that promote the differentiation of T lymphocytes. The principal costimulators for T cells are the B7 molecules (CD80 and CD86) expressed by professional APCs and recognized by the CD28 receptor on naive T cells. The innate immune response to polysaccharides also results in the activation of complement, generating cleavage products that promote the differentiation of B lymphocytes. Thus, antigen (signal 1 in Fig. 5-3) and molecules produced during the innate immune response (signal 2) function cooperatively to activate antigen-specific lymphocytes. The requirement for microbe-induced adaptive immune response is induced by microbes and not by harmless substances.

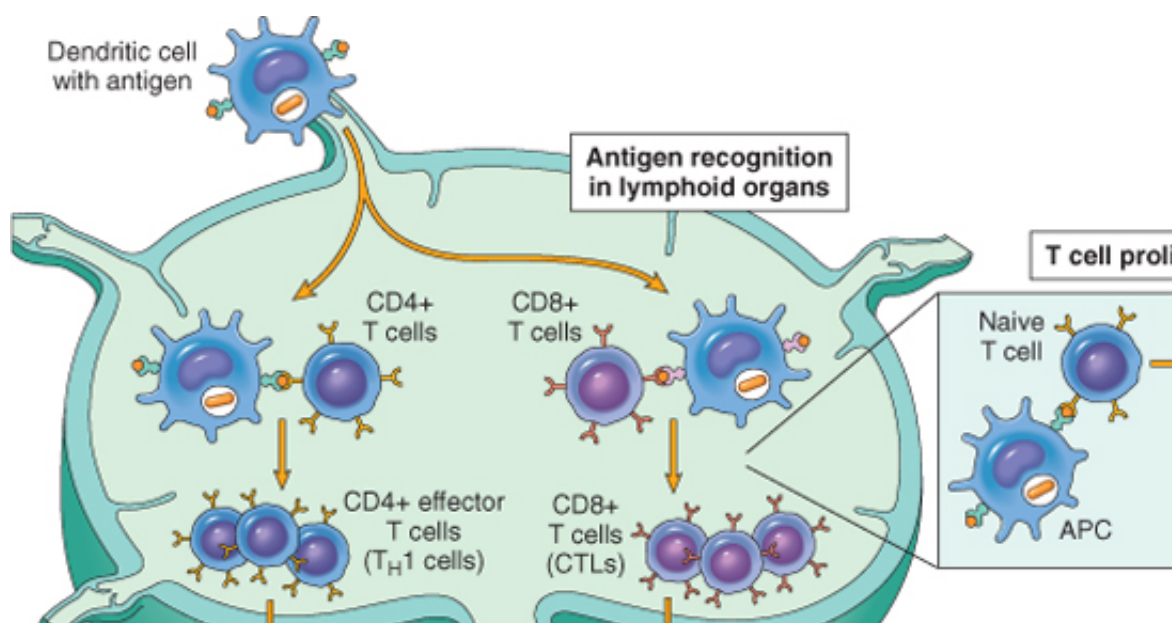
Antigen recognition and costimulation together trigger the functional responses of the antigen-specific lymphocytes. These responses proceed in steps, which are also reflected in the sequence of events in adaptive immune responses. In all immune responses, the reactions of T and B lymphocytes differ in important ways.

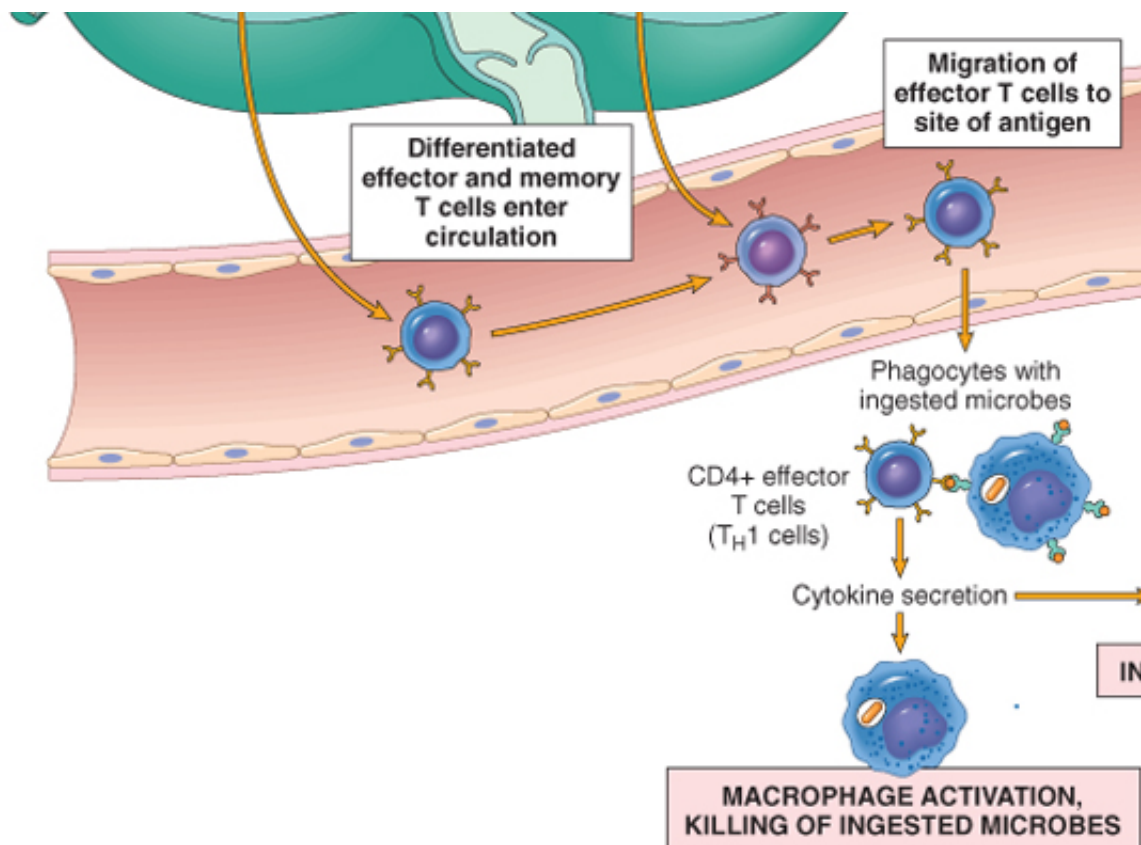
**Cell-Mediated Immunity: Activation of T Lymphocytes and Elimination of Cell-Associated Antigens**

## Cell-mediated immunity: Activation of T Lymphocytes and Elimination of Cell-Associated Antigen



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 Figure 5-5 Adaptive immune responses consist of sequential phases: recognition of antigen by specific lymphocytes (proliferation and differentiation into effector cells), and the effector phase (elimination of antigen). The response of antigen-stimulated lymphocytes die by apoptosis. The antigen-specific cells that survive are responsible for mediating different immune responses. The y-axis represents an arbitrary measure of the magnitude of the response. These responses include humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).





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Figure 5-6 Cell-mediated immunity. Naive T cells recognize MHC-associated peptide antigens displayed on dendritic cells and proliferate (under the influence of the cytokine IL-2) and to differentiate into effector and memory cells, which perform functions in cell-mediated immunity. Effector CD4+ T cells of the  $T_H1$  subset recognize the antigens of microbial phagocytes to kill the microbes and induce inflammation. CD8+ CTLs kill infected cells harboring microbes in the tissue, which is especially important in defense against helminthic infections. Some activated T cells differentiate into long-lived

Naive T lymphocytes are activated by antigen and costimulators in peripheral lymphoid organs, and effector cells that migrate to any site where the antigen (microbe) is present (Fig. 5-6). Upon activation, they secrete proteins called *cytokines*, which function as growth and differentiation factors for lymphocytes and other leukocytes. Because of the important roles of cytokines in immune responses and inflammatory diseases, it is important to understand their properties and actions.

### **Cytokines: Messenger Molecules of the Immune System**

Cytokines are polypeptide products of many cell types (but principally activated lymphocytes and macrophages) that mediate inflammation and immune responses. They were introduced in Chapter 2 in the context of inflammatory responses and focus on those cytokines specifically involved in adaptive immunity.

Although different cytokines have diverse actions and functions, they all share some common features: they are secreted in response to external stimuli, which may be microbial products, antigen recognition, or tissue damage; their secretion is typically transient and is controlled by transcription and post-translational mechanisms. The action of a cytokine is determined by the cell that produces the cytokine, the target cell (paracrine (on adjacent cells), and, less commonly, endocrine (at a distance)). The effects of cytokines tend to be *pleiotropic* (one cytokine has effects on many cell types) and *redundant* (induced by many proteins).

Cytokines may be grouped into several classes based on their biologic activities and functions.

*Cytokines involved in innate immunity and inflammation*, the earliest host response to micro



in this group are TNF and interleukin-1 (IL-1), a group of chemoattractant cytokines called chemokines. The sources of these cytokines are activated macrophages and DCs, as well as endothelial cell types. These were described in [Chapter 2. Cytokines that regulate lymphocyte responses and immunity](#). Different cytokines are involved in the proliferation and differentiation of lymphocytes. Activation of various effector cells (e.g., IFN- $\gamma$ , which activates macrophages, and IL-5, which activates eosinophils; and IL-13, which activates mucosal epithelial cells to secrete mucus and exocytosis). It has been described recently that produces the cytokine IL-17, which promotes inflammation, and some T cell-mediated inflammatory disorders. These effector cells migrate to sites of infection and the differentiated effectors again encounter cell-associated microbes, they are activated to perform elimination of the microbes. The key mediators of the functions of helper T cells are the surface molecules which binds to its receptor, CD40, on B cells and macrophages, and various cytokines. Differentiated subset recognize microbial peptides on macrophages that have ingested the microbes. The T cell on the macrophages, and the T cells secrete the cytokine, IFN- $\gamma$ , which is a potent macrophage activator. IFN- $\gamma$ -mediated activation results in the induction of potent microbicidal substances in the macrophage and **nitric oxide**, leading to the destruction of ingested microbes. T<sub>H</sub>2 cells elicit cellular defense of eosinophils and not macrophages. As we discuss below, CD4+ helper T cells also stimulate B-cell

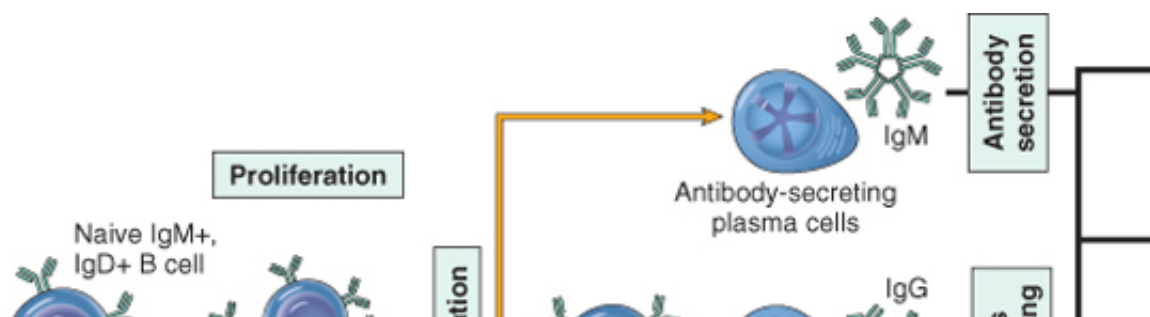
### Effector Functions of T Lymphocytes

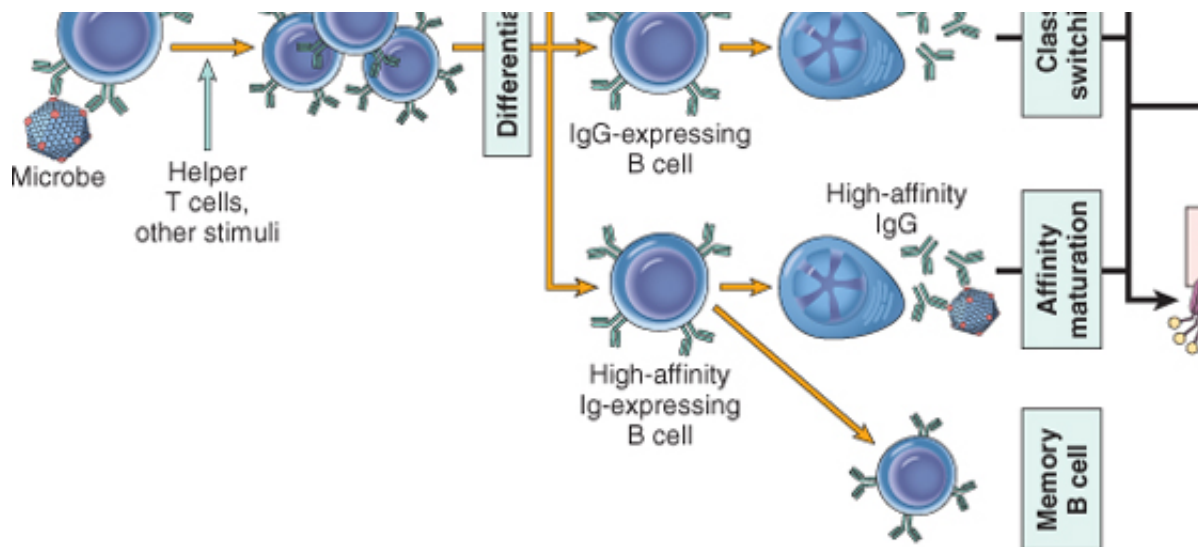
One of the earliest responses of CD4+ helper T cells is secretion of the cytokine IL-2 and expression of a growth factor that acts on these T lymphocytes and stimulates their proliferation, leading to a large pool of specific lymphocytes. Some of the progeny of the expanded pool of T cells differentiate into effector cells that secrete cytokines and thus perform different functions. *The best defined subsets of CD4+ helper cells are* T<sub>H</sub>1 cells, which produce the cytokine IFN- $\gamma$ , which activates macrophages and stimulates B cells to produce antibodies against microbes for phagocytosis. T<sub>H</sub>2 cells produce IL-4, which stimulates B cells to differentiate into IgE-secreting cells; IL-5, which activates eosinophils; and IL-13, which activates mucosal epithelial cells to secrete mucus and exocytosis. It has been described recently that produces the cytokine IL-17, which promotes inflammation, and some T cell-mediated inflammatory disorders. These effector cells migrate to sites of infection and the differentiated effectors again encounter cell-associated microbes, they are activated to perform elimination of the microbes. The key mediators of the functions of helper T cells are the surface molecules which binds to its receptor, CD40, on B cells and macrophages, and various cytokines. Differentiated subset recognize microbial peptides on macrophages that have ingested the microbes. The T cell on the macrophages, and the T cells secrete the cytokine, IFN- $\gamma$ , which is a potent macrophage activator. IFN- $\gamma$ -mediated activation results in the induction of potent microbicidal substances in the macrophage and **nitric oxide**, leading to the destruction of ingested microbes. T<sub>H</sub>2 cells elicit cellular defense of eosinophils and not macrophages. As we discuss below, CD4+ helper T cells also stimulate B-cell

Activated CD8+ lymphocytes differentiate into CTLs that kill cells harboring microbes in the cytoplasm. CTLs can kill many cell types, or bacteria that are ingested by macrophages but have learned to escape the macrophage cytoplasm (where they are inaccessible to the killing machinery of phagocytes, which is largely confined to the cytoplasm of infected cells, CTLs eliminate the reservoirs of infection).

### Humoral Immunity: Activation of B Lymphocytes and Elimination of Extracellular Microbes

Upon activation, B lymphocytes proliferate and then differentiate into plasma cells that secrete different types of antibodies (Fig. 5-7). Many polysaccharide and lipid antigens have multiple identical antigenic determinants that can engage several antigen receptor molecules on each B cell and initiate the process of B-cell activation. Protein antigens are not able to bind to many antigen receptors, and the full response of B cells to protein antigens requires the help of T cells. The helper T cells express CD40L and secrete cytokines, which work together to activate B cells.





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 Figure 5-7 Humoral immunity. Naive B lymphocytes recognize antigens, and under the influence of helper T cell activated to proliferate and to differentiate into antibody-secreting plasma cells. Some of the activated B cells undergo affinity maturation, and some become long-lived memory cells. Antibodies of different heavy-chain isotypes (classes) are produced on the right.

Some of the progeny of the expanded B-cell clones differentiate into antibody-secreting plasma cells that have the same antigen binding site as the cell surface antibodies (B-cell receptors) that first recognized the antigen. Protein antigens, by virtue of CD40L- and cytokine-induced proliferation, induce the production of antibodies of different classes (IgG, IgA, IgE). This production of functionally different antibodies, called *heavy-chain class (isotype) switching*, provides plasticity in the antibody response. Helper T cells also stimulate the production of antibodies with higher and higher affinity. *Affinity maturation*, improves the quality of the humoral immune response.

The humoral immune response combats microbes in numerous ways (see Fig. 5-7).

Antibodies bind to microbes and prevent them from infecting cells, thus "neutralizing" the microbes. IgG and IgM activate the complement system by the classical pathway, and complement destruction of microbes. Most opsonizing and complement-fixing IgG antibodies are stimulated by many bacteria and viruses, and IgG antibodies are important mechanisms of defense against mucosal tissues and neutralizes microbes in the lumens of the respiratory and gastrointestinal tissues). IgG is actively transported across the placenta and protects the newborn until the infant's own antibodies develop. IgG coats helminthic parasites, and functions with mast cells and eosinophils to kill the parasite. IgE secretes cytokines that stimulate the production of IgE and activate eosinophils, and thus the response by T<sub>H</sub>2 cells.

Most circulating antibodies have half-lives of about 3 weeks. Some antibody-secreting plasma cells can survive for years, continuing to produce low levels of antibodies.

### **Decline of Immune Responses and Immunologic Memory**

The majority of effector lymphocytes induced by an infectious pathogen die by apoptosis after the immune system returns to its basal resting state. This return to a stable or steady state is called homeostasis. Essential stimuli for lymphocyte survival and activation and effector cells are short-lived. Therefore, activated lymphocytes are no longer kept alive.

The initial activation of lymphocytes also generates long-lived memory cells, which may survive for years or even decades, ready to respond to a subsequent encounter with the same antigen.

are an expanded pool of antigen-specific lymphocytes (more numerous than the naive cells specific for that antigen), and memory cells respond faster and more effectively against the antigen. The generation of memory cells is an important goal of vaccination.

This brief discussion of the normal immune response sets the stage for a consideration of the situation when the immune response becomes abnormal, and how these abnormalities lead to tissue injury and disease.

## SUMMARY

### Overview of Normal Immune Responses

The physiologic function of the immune system is defense against infectious agents. The reaction to microbes is mediated by the mechanisms of *innate immunity*, which is present from birth. These mechanisms include epithelial barriers, phagocytes, NK cells, and proteins, e.g., of the complement system. The reaction of innate immunity is *inflammation*. The defense reactions of *adaptive immunity* develop slowly, but are highly specialized. Microbes and other foreign antigens are captured by dendritic cells in lymph nodes, where the antigens are recognized by naïve lymphocytes. They are then activated to proliferate and differentiate into effector and memory cells. *Cell-mediated immunity* is the reaction of T lymphocytes, designed to combat cell-associated microbes (e.g., viruses and microbes in the cytoplasm of infected cells). *Humoral immunity* is the reaction of B lymphocytes, which produce antibodies and is effective against extracellular microbes (in the circulation and body lumens). CD4<sup>+</sup> helper T cells help B cells to make antibodies, activate macrophages to ingest microbes, and regulate all immune responses to protein antigens. Cytotoxic T cells are mediated by secreted proteins called *cytokines*. CD8<sup>+</sup> cytotoxic T cells kill cells that express antigens in the cytoplasm that are seen as foreign (e.g. virus-infected cells). Antibodies secreted by plasma cells neutralize microbes and block the attachment of microbes to cells. They also promote the phagocytosis and destruction of pathogens. Antibodies also confer passive immunity.



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## HYPERSENSITIVITY DISEASES: MECHANISMS OF IMMUNE-MEDIATED IN

Immune responses are capable of causing tissue injury and diseases that are called *hypersensitivity*. The idea that individuals who mount immune responses against an antigen are said to be "sensitized" to that antigen. Pathologic or excessive reactions are manifestations of "hypersensitivity." Normally, an exquisite immune response is sufficient for the eradication of infecting organisms without serious injury to host tissues. However, immune responses can be directed against self or inappropriately targeted to host tissues, and in these situations, the normally beneficial responses become pathologic. In the following sections, we will describe the causes and general mechanisms of hypersensitivity diseases, and the immune response is responsible for the disease.

### Causes of Hypersensitivity Diseases

Pathologic immune responses may be directed against different types of antigens, and may result in different types of tissue injury.

**Autoimmunity.** Normally, the immune system does not react against an individual's own antigens. This is called *self-tolerance*, implying that all of us "tolerate" our own antigens. Sometimes, self-tolerance fails, and the immune system attacks cells and tissues that are called *autoimmunity*. The diseases caused by autoimmunity are reviewed in Chapter 13. We will return to the mechanisms of self-tolerance and autoimmunity later in this chapter. **Reactions against microbial antigens.** Some types of reactions against microbial antigens that may cause disease. In some cases, the immune response is directed against a microbial antigen that is unusually persistent. If antibodies are produced against such antigens, they can form immune complexes, which deposit in tissues and trigger inflammation; e.g., *poststreptococcal glomerulonephritis* (Chapter 14). T-cell responses against persistent microbes can cause chronic inflammation, sometimes with the formation of granulomas (Chapter 2); this is the cause of *tuberculosis*. Rarely, antibodies or T cells reactive with a microbe cross-react with a host tissue, as in *rheumatic heart disease* (Chapter 11). Sometimes the disease-causing immune response is directed against host tissues. In *viral hepatitis*, the virus that infects liver cells is recognized as foreign by the immune system. Cytotoxic T cells try to eliminate infected cells, but in the process, they damage liver cells. **Reactions against environmental antigens.** Most healthy individuals do not react to environmental substances (e.g., pollens, animal danders, or dust mites), but almost 20% of the population does. Allergies are diseases caused by unusual immune responses to a variety of non-infectious antigens to which all individuals are exposed but against which only some react.

In all these conditions, tissue injury is caused by the same mechanisms that normally function to protect the body. Antibodies, effector T lymphocytes, and various other effector cells are involved. The problem in these diseases is that the immune response is maintained inappropriately. Because the stimuli for these abnormal immune responses are difficult to eliminate (e.g., persistent microbes, or environmental antigens), and the immune system has many intrinsic amplification mechanisms, once a pathologic immune response starts it is difficult to control or terminate. Hypersensitivity diseases tend to be chronic, often debilitating, and are therapeutic challenges. Since inflammation is a major component of the pathology of these disorders, they are sometimes grouped as *inflammatory diseases*.

### Types of Hypersensitivity Diseases

Hypersensitivity reactions are traditionally subdivided into four types; three are variations on antibody-mediated reactions (Table 5-1). The rationale for this classification is that the mechanism of immune injury is different for each type, and may even help to guide the therapy. However, this classification of immune-mediated diseases is not perfect, because several immune reactions may coexist in one disease.

**Immediate (type I) hypersensitivity** results from the activation of the  $T_H2$  subset of  $CD4^+$  helper T cells, leading to the production of IgE antibodies, which become attached to mast cells. When the antigen (allergen) is encountered, the mast cells are triggered to release mediators that transiently affect vascular permeability and smooth muscle contraction, leading to the characteristic symptoms of allergic reactions.



contraction in various organs, and may stimulate more prolonged inflammation (the late phase commonly called *allergies*). *Antibody-mediated (type II) hypersensitivity* disorders are caused by cell surface antigens and promote phagocytosis and destruction of the coated cells or trigger tissues. *Immune complex-mediated (type III) hypersensitivity* disorders are caused by antibody complexes that circulate and may deposit in vascular beds and stimulate inflammation, T cell activation. Tissue injury in these diseases is the result of the inflammation. *T-cell-mediated* cell-mediated immune responses in which T lymphocytes cause tissue injury, either by proliferate and activate macrophages, or by directly killing host cells.

**Table 5-1. Mechanisms of Immunologically Mediated Diseases**

Type	Prototype Disorder	Immune Mechanisms
Immediate (type I) hypersensitivity	Anaphylaxis, allergies, bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)
Antibody-mediated (type II) hypersensitivity	Autoimmune hemolytic anemia; Goodpasture syndrome	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes
Immune complex-mediated (type III) hypersensitivity	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules
T-cell-mediated (type IV) hypersensitivity	Contact dermatitis; multiple sclerosis; type I diabetes; transplant rejection; tuberculosis	Activated T lymphocytes → (i) release of cytokines and macrophage activation; (ii) T-cell-mediated cytotoxicity

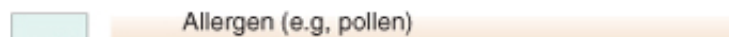
### Immediate (Type I) Hypersensitivity

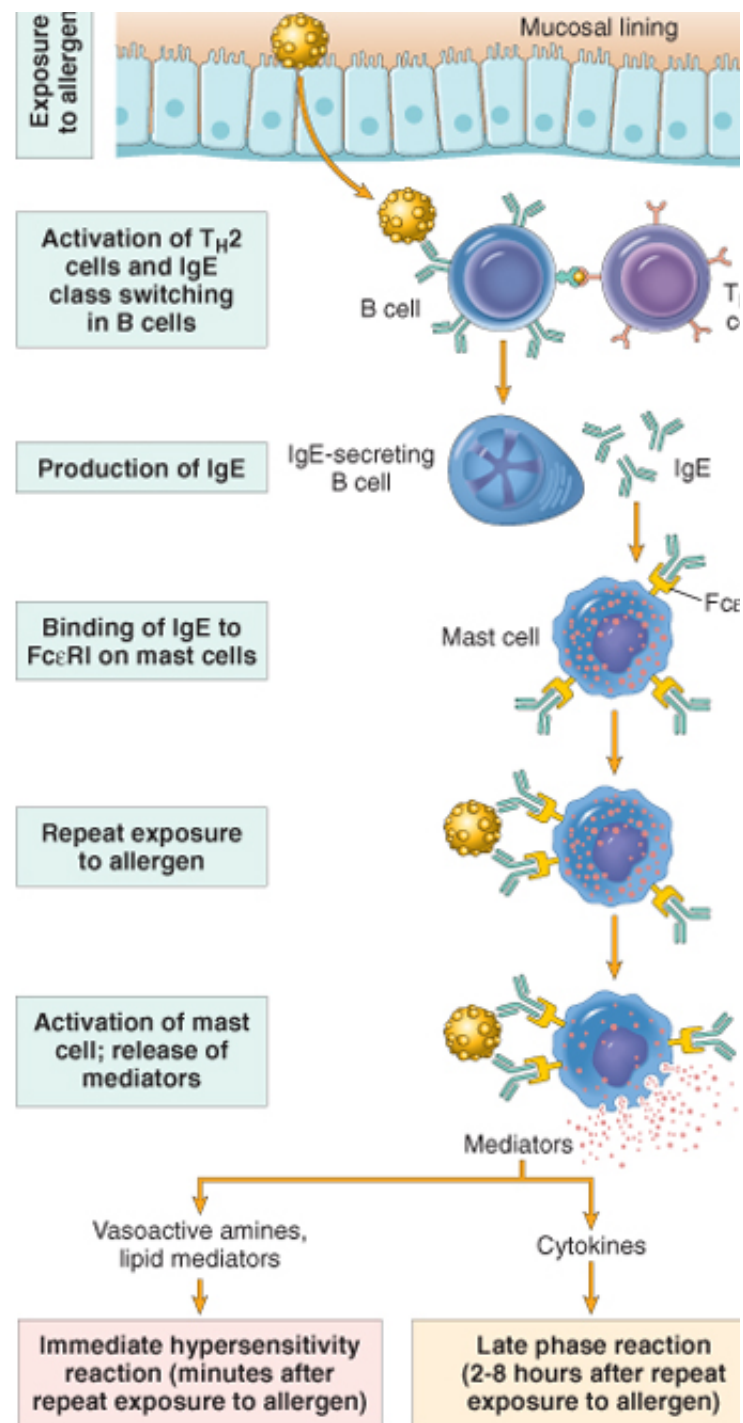
Immediate hypersensitivity is a tissue reaction that occurs rapidly (typically within minutes) after the allergen is bound to the surface of mast cells in a sensitized host. The reaction is initiated by entry of the allergen into the tissue because it triggers allergy. Many allergens are environmental substances that are harmless for most people, but some people apparently inherit genes that make them susceptible to allergies. This susceptibility is manifested by the ability to make strong  $T_H2$  responses and, subsequently, IgE antibody against the allergens. The IgE is bound to the surface of mast cells, and release of mediators that are responsible for the clinical and pathologic manifestations of the reaction. The reaction can occur as a local reaction that is merely annoying (e.g., seasonal rhinitis, or hay fever) or severely as a fatal systemic disorder (anaphylaxis).

### Sequence of Events in Immediate Hypersensitivity Reactions

Most hypersensitivity reactions follow the same sequence of cellular responses (Fig. 5-8).

**Activation of  $T_H2$  cells and production of IgE antibody.** Allergens may be introduced by inhalation, ingestion, or injection. Factors that probably contribute to the strong  $T_H2$  responses to allergens include the route of entry, the timing of exposure; the absence of inflammation and innate immunity at the time of allergen recognition. It is not clear if allergenic substances also have unique structural properties that endow them with high affinity for the  $T_H2$  cells. The  $T_H2$  cells that are induced secrete several cytokines that are responsible for essential features of allergic hypersensitivity. IL-4 stimulates B cells specific for the allergen to undergo heavy-chain class switching to the IgE isotype. IL-5 activates eosinophils that are recruited to the reaction, and IL-13 acts on epithelial cells to increase mucin secretion.  $T_H2$  cells are often recruited to the site of allergic reactions in response to chemokines. One of these chemokines is eotaxin, which also recruits eosinophils to the same site.





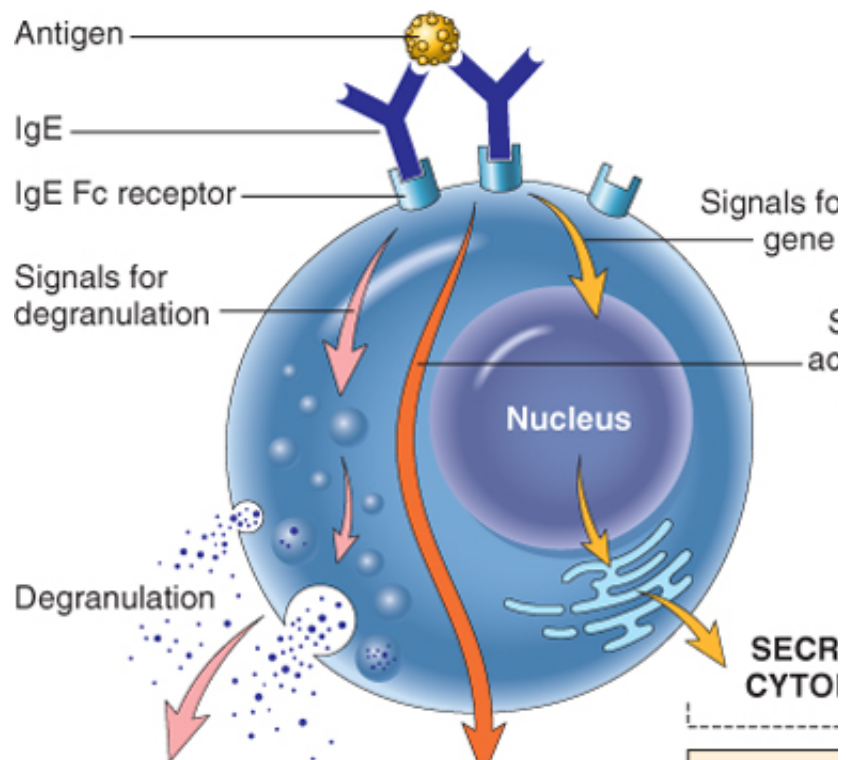
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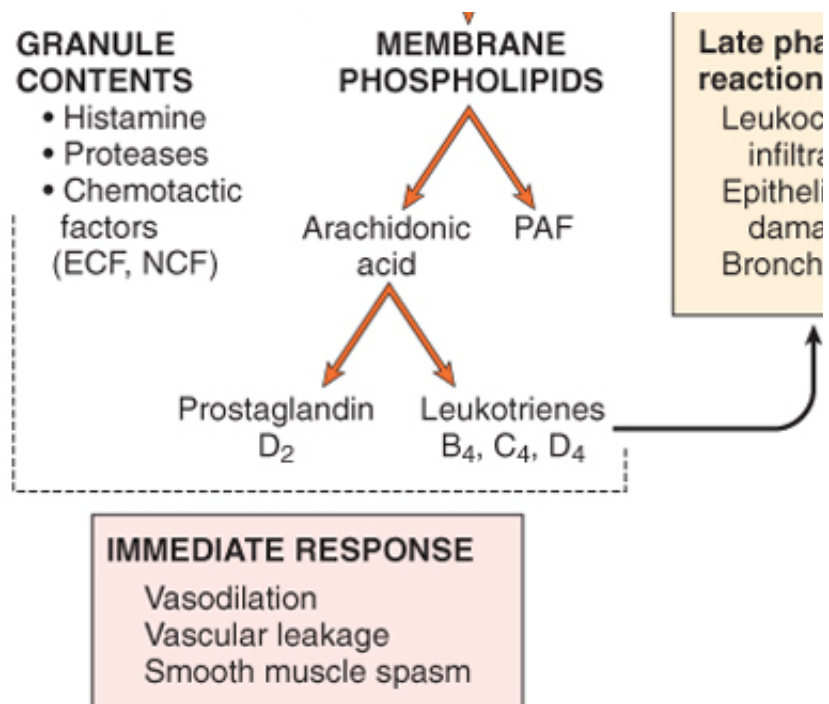
Figure 5-8 Sequence of events in immediate (type 1) hypersensitivity. Immediate hypersensitivity reactions are initiated by allergen exposure, which stimulates  $T_H2$  responses and IgE production. IgE binds to Fc receptors (Fc $\epsilon$ RI) on mast cells, and subsequent exposure to allergen stimulates mast cells to secrete the mediators that are responsible for the pathologic manifestations of immediate hypersensitivity.

The central role of  $T_H2$  cells and IgE antibody in immediate hypersensitivity reactions is well established by experimental studies. Levels of serum IgE (and, in some studies, the numbers of  $T_H2$  cells in the blood) are elevated in patients who suffer from allergies, and reducing IgE levels is of therapeutic benefit.

**Sensitization of mast cells by IgE antibody.** Mast cells are derived from bone marrow, are v reside near blood vessels and nerves and in subepithelial locations. Mast cells express a h the  $\epsilon$  heavy chain of IgE, called Fc $\epsilon$ RI. Even though the serum concentration of IgE is very affinity of the mast cell Fc $\epsilon$ RI receptor is so high that it is always occupied by IgE. These are "sensitized" to react if the antigen binds to the antibody molecules. Basophils are the circ also express Fc $\epsilon$ RI, but their role in most immediate hypersensitivity reactions is not establ tissues and not in the circulation). The third cell type that expresses Fc $\epsilon$ RI are eosinophils, reactions and also have a role in IgE-mediated host defense against helminth infections, d and release of mediators. When individuals who were sensitized by exposure to an allergen to multiple specific IgE molecules on mast cells, usually at or near the site of allergen entry linked, a series of biochemical signals is triggered in the mast cells. The signals culminate the mast cells. Three groups of mediators are the most important in different immediate hy

**Vasoactive amines released from granule stores.** The granules of mast cells contain seconds or minutes of activation. Histamine causes vasodilation, increased vascula contraction, and increased secretion of mucus. Other rapidly released mediators inc bronchoconstriction and inhibits platelet aggregation) and chemotactic factors for ne granule contents that may be secreted include several neutral proteases (e.g., trypt; generate kinins and cleave complement components to produce additional chemot Chapter 2). The granules also contain acidic proteoglycans (heparin, chondroitin su to be as a storage matrix for the amines. **Newly synthesized lipid mediators.** Mast ce and leukotrienes, by the same pathways as do other leukocytes (Chapter 2). These are important in immediate hypersensitivity reactions. **Prostaglandin  $D_2$  ( $PGD_2$ )** is th the cyclooxygenase pathway in mast cells. It causes intense bronchospasm as well **Leukotrienes  $C_4$  and  $D_4$  ( $LTC_4$ ,  $LTD_4$ )** are the most potent vasoactive and spasmog they are several thousand times more active than histamine in increasing vascular p smooth muscle contraction.  **$LTB_4$**  is highly chemotactic for neutrophils, eosinophils, mast cells results in the synthesis and secretion of several cytokines that are import include TNF and chemokines, which recruit and activate leukocytes (Chapter 2), IL- initiated immune reaction, and IL-13, which stimulates epithelial cell mucus secretio





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 Figure 5-9 Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible for the immediate and late phase reactions. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor (neither of these has been biochemically identified).

**Table 5-2. Summary of the Action of Mast Cell Mediators in Immediate (Type I) Hypersensitivity Reaction**

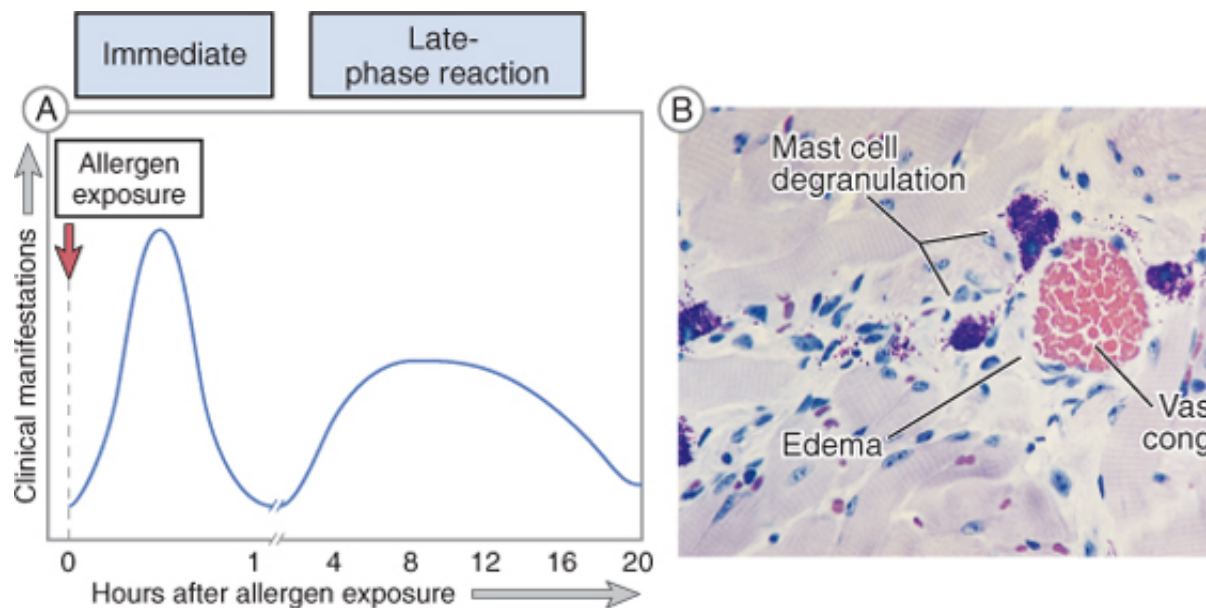
Action	Mediator
Vasodilation, increased vascular permeability	Histamine PAF Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub> Neutral proteases that activate complement and kinin Prostaglandin D <sub>2</sub>
Smooth muscle spasm	Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub> Histamine Prostaglandins PAF
Cellular infiltration	Cytokines (e.g., chemokines, TNF) Leukotriene B <sub>4</sub> Eosinophil and neutrophil chemotactic factors (not shown)

PAF, platelet-activating factor; TNF, tumor necrosis factor.

In summary, a variety of compounds that act on blood vessels, smooth muscle, and leukocytes mediate the allergic response (Table 5-2). Some of these compounds are released rapidly from sensitized mast cells and are responsible for the immediate reactions associated with conditions such as systemic anaphylaxis. Others, such as cytokines, are involved in late-phase reactions.

**Late-phase reactions.** Often, the IgE-triggered reaction has two well-defined phases (Fig. 5-9). The first phase is characterized by vasodilation, vascular leakage, and smooth muscle spasm, usually evident within minutes of allergen exposure and subsiding by 60 minutes; and (2) a second, late-phase reaction that usually occurs 4–6 hours after allergen exposure and lasts for several days and is characterized by inflammation as well as tissue destruction, such as airway hyperresponsiveness. The dominant inflammatory cells in the late-phase reaction are neutrophils, eosinophils, and lymphocytes. Neutrophils are recruited by various chemokines; their roles in inflammation were described in Chapter 4.

by eotaxin and other chemokines released from TNF-activated epithelium and are important in the late-phase response. Eosinophils produce major basic protein and eosinophil cationic protein, as well as LTC<sub>4</sub> and platelet-activating factor, which promote inflammation. Cytokines produced by T<sub>H</sub>2 cells are also described above. The recruited leukocytes can amplify and sustain the inflammatory response after allergen exposure. In addition, inflammatory leukocytes are responsible for much of the epithelial hyperplasia in allergic diseases. Because inflammation is a major component of many allergic diseases, non-pharmacologic therapy usually includes anti-inflammatory drugs such as corticosteroids.



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 Figure 5-10 Immediate hypersensitivity. **A**, Kinetics of the immediate and late-phase reactions. The immediate reaction develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops within hours. **B**, Morphology: The immediate reaction is characterized by vasodilation, congestion, and edema, and the late-phase reaction is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Micrographs courtesy of Dr. Daniel Friend, DeBartolo Hospital, Boston, Massachusetts.)

### Clinical and Pathologic Manifestations

An immediate hypersensitivity reaction may occur as a systemic disorder or as a local reaction. The type of reaction is determined by the route of antigen exposure. Systemic (parenteral) administration of protein antigens (e.g., penicillin) may result in *systemic anaphylaxis*. Within minutes of an exposure in a sensitized host, erythema appears, followed in short order by profound respiratory difficulty caused by pulmonary bronchoconstriction and hypersecretion of mucus. Laryngeal edema may exacerbate matters by causing upper airway obstruction. The entire gastrointestinal tract may be affected, with resultant vomiting, abdominal cramps, and diarrhea. There may be systemic vasodilation with fall in blood pressure (*anaphylactic shock*), and the patient may die within minutes.

**Local reactions** generally occur when the antigen is confined to a particular site, such as skin (contact dermatitis), gut (ingestion, causing diarrhea), or lung (inhalation, causing bronchoconstriction). The common cold, hay fever, and certain forms of asthma are examples of localized allergic reactions.

Susceptibility to localized type I reactions is genetically controlled, and the term *atopy* is used to describe individuals who are prone to localized reactions. Patients who suffer from nasobronchial allergy (including hay fever and some forms of asthma) often have a family history of similar conditions. Linkage studies have identified several chromosomal regions that are associated with allergic diseases. Among the candidate genes that are present close to these chromosomal regions are molecules (which may confer immune responsiveness to particular allergens), cytokines (which may regulate the response), and the FcεRI, and ADAM33, a metalloproteinase that may be involved in tissue remodeling in the airways.



Before this discussion of immediate hypersensitivity is closed, it is worth noting that these reactions cause human discomfort and disease. The immune response dependent on  $T_H2$  cells and IgE, in particular, plays an important protective role in parasitic infections. IgE antibodies are produced in response to parasitic antigens; their physiologic function is to target helminths for destruction by eosinophils and mast cells. Mast cells also play a role in bacterial infections. And snake aficionados will be relieved to hear that their mast cells may protect them by releasing granule proteases that degrade the toxins. Why these beneficial responses are inappropriate to environmental antigens, giving rise to allergies, remains a puzzle.

## SUMMARY

### Immediate (Type I) Hypersensitivity

Also called allergic reactions, or allergies. Induced by environmental antigens. Strong  $T_H2$  responses and IgE production in genetically susceptible individuals. Binding to Fcε receptors; re-exposure to the allergen leads to cross-linking and activation of mast cells, and release of mediators. Principal mediators are histamine and other granule contents; prostaglandins and leukotrienes; cytokines. Mediators cause immediate vascular and smooth muscle reactions and the late-phase reactions. Clinical manifestations may be local or systemic, and range from mildly annoying to fatal anaphylaxis.

### Antibody-Mediated Diseases (Type II Hypersensitivity)

Antibody-mediated (type II) hypersensitivity disorders are caused by antibodies directed against target antigens on other tissue components. The antigens may be normal molecules intrinsic to cell membranes or exogenous antigens (e.g., a drug metabolite). Antibody-mediated abnormalities are the diseases; examples of these are listed in Table 5-3. In all these disorders the tissue damage or dysfunction is caused by a limited number of mechanisms.

### Mechanisms of Antibody-Mediated Diseases

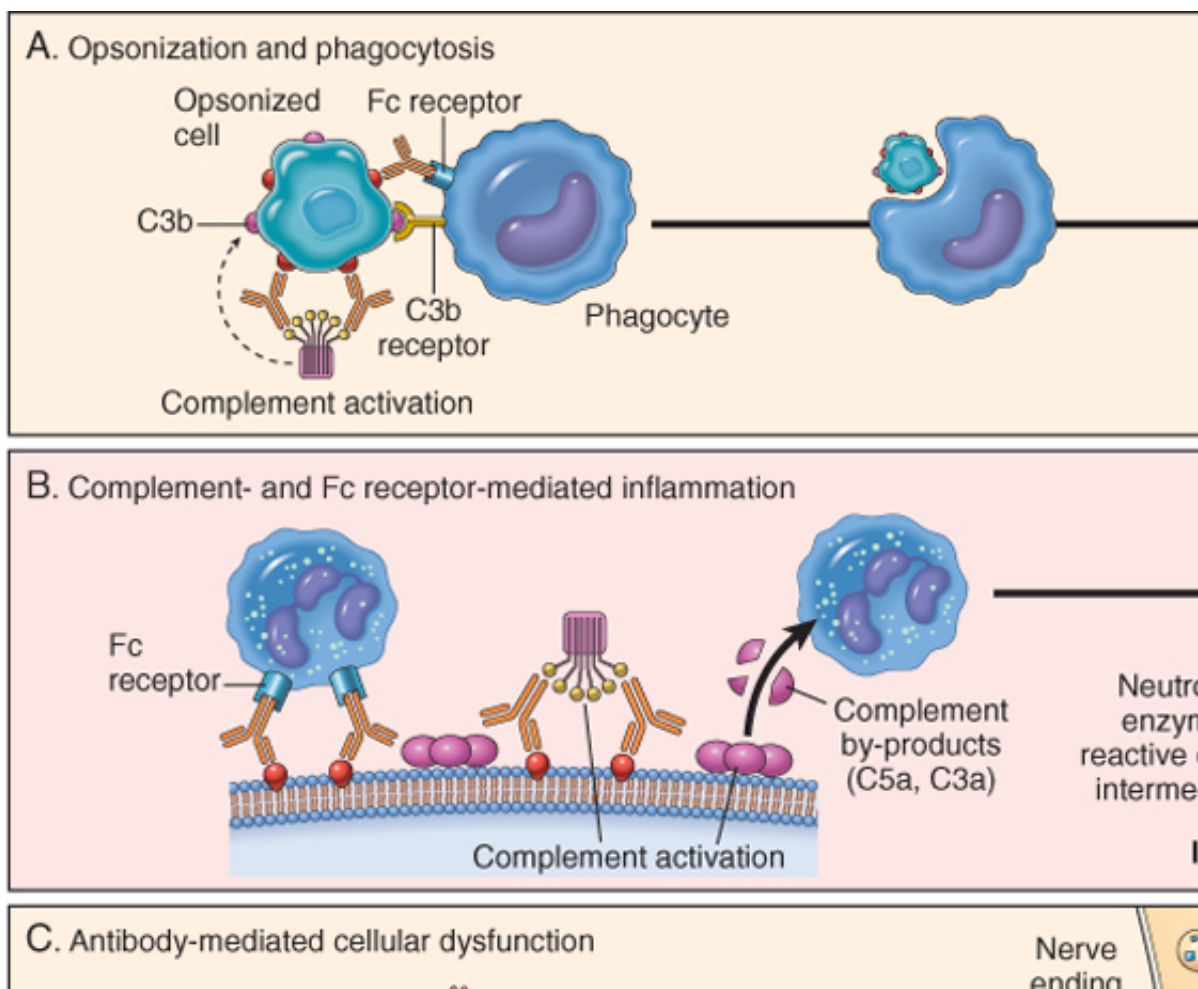
**Table 5-3. Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)**

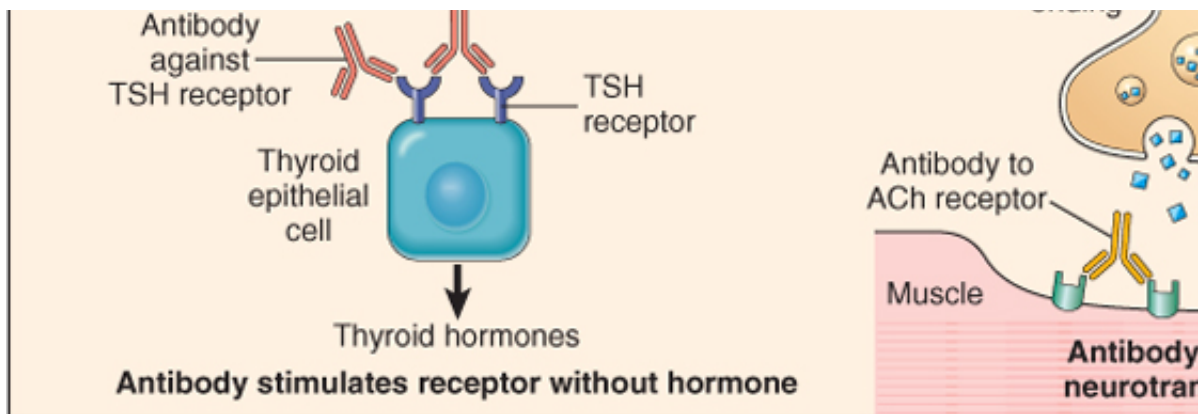
Disease	Target Antigen	Mechanisms of Disease
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIb:IIIa integrin)	Opsonization and phagocytosis of platelets
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation and disruption of intercellular adhesion
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor-mediated inflammation
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding to receptors
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of receptors
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin to receptors
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor

ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Antibodies cause disease by targeting cells for phagocytosis, by activating the complement system functions (Fig. 5-11). The antibodies that are responsible are typically high-affinity antibodies capable of binding to the Fc receptors of phagocytes.

**Opsonization and phagocytosis.** When circulating cells, such as erythrocytes or platelets, are coated with autoantibodies, with or without complement proteins, the cells become targets for phagocytosis (see Fig. 5-11A). These phagocytes express receptors for the Fc tails of IgG antibodies and for complement protein, and use these receptors to bind and ingest opsonized particles. Opsonization occurs in the spleen, and this is why splenectomy is of some benefit in autoimmune thrombocytopenia and in autoimmune hemolytic anemia. Antibodies bound to cellular or tissue antigens activate the complement system by the "classical" pathway. Complement activation recruits neutrophils and monocytes, triggering inflammation in tissues. Complement proteins can lyse cells, especially erythrocytes. Leukocytes may also be activated by engagement of Fc receptors and complement receptors. **Antibody-mediated cellular dysfunction.** In some cases, antibodies directed against cell surface receptors dysregulate cellular function without causing cell injury or inflammation (Fig. 5-11C). In myasthenia gravis, antibodies directed against acetylcholine receptors in the motor end plates of skeletal muscles inhibit neuromuscular transmission, causing muscle weakness. Antibodies can also stimulate cell function inappropriately. In Graves' disease, antibodies directed against the thyroid-stimulating hormone receptor stimulate thyroid epithelial cells to secrete thyroid hormones, resulting in hyperthyroidism. In some cases, antibodies can neutralize and block the actions of these molecules.





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Figure 5-11 Effector mechanisms of antibody-mediated injury. **A**, Opsonization of cells by antibodies and complement by phagocytes. **B**, Inflammation induced by antibody binding to Fc receptors of leukocytes and by complement binding to cells. In these examples, antibodies against the thyroid-stimulating hormone receptor cause hyperthyroidism, and acetylcholine (ACh) receptor antibodies impair neuromuscular transmission.

## SUMMARY

### Pathogenesis of Diseases Caused by Antibodies and Immune Complexes

Antibodies can coat (opsonize) cells, with or without complement proteins, and cause *phagocytosis* by phagocytes (macrophages), which express receptors for the complement proteins. The result is depletion of the opsonized cells. Antibody complexes may deposit in tissues or blood vessels, and elicit an *acute inflammation* by activating complement, with release of breakdown products, or by engaging leukocytes. The inflammatory reaction causes tissue injury. Antibodies can block receptors or essential molecules, and cause *functional derangements* (either activation or inhibition) without cell injury.

### Immune Complex Diseases (Type III Hypersensitivity)

Antigen-antibody (immune) complexes that are formed in the circulation may deposit in blood vessels and cause acute inflammation. The antigens in these complexes may be exogenous antigens, such as drugs, or endogenous antigens, such as nucleoproteins. The mere formation of immune complexes does not equate with disease. Immune complexes are produced during many immune responses and are usually phagocytosed for antigen removal. It is only when these complexes are produced in large amounts, persist, and are pathogenic. Pathogenic immune complexes may form in the circulation and subsequently deposit in tissues. Immune complex-mediated diseases are formed in the circulation and are deposited in several organs, or localized to particular organs. The mechanism of tissue injury is the same in all cases, but the sequence of events and the conditions leading to the formation of systemic and localized immune complex diseases can be considered separately. Immune complex diseases are some of the most common immunologic diseases.

Table 5-4. Examples of Immune Complex-Mediated Diseases

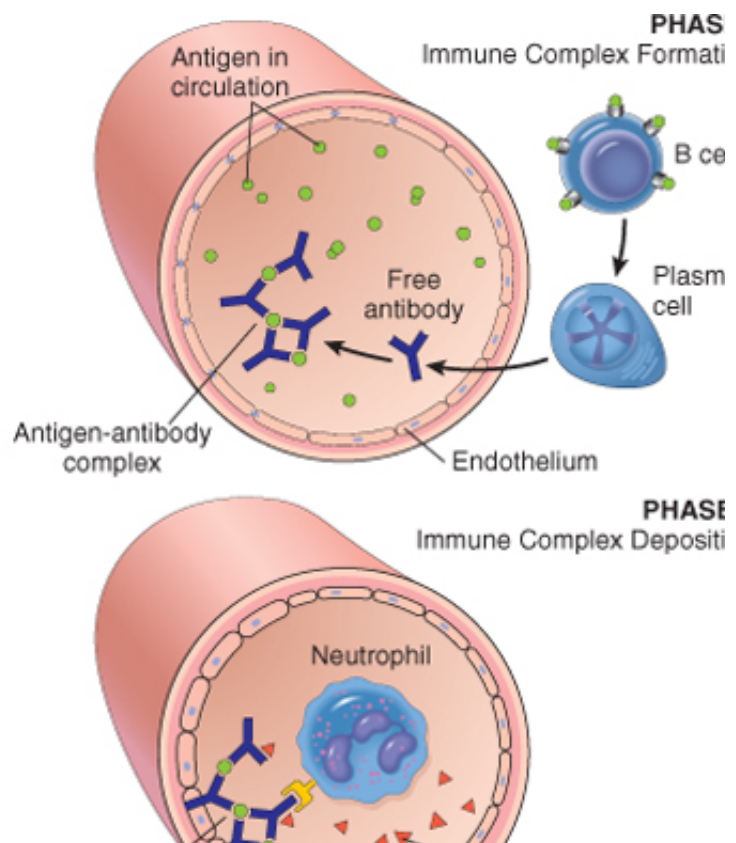
Disease	Antigen Involved
Systemic lupus erythematosus	Nuclear antigens
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane

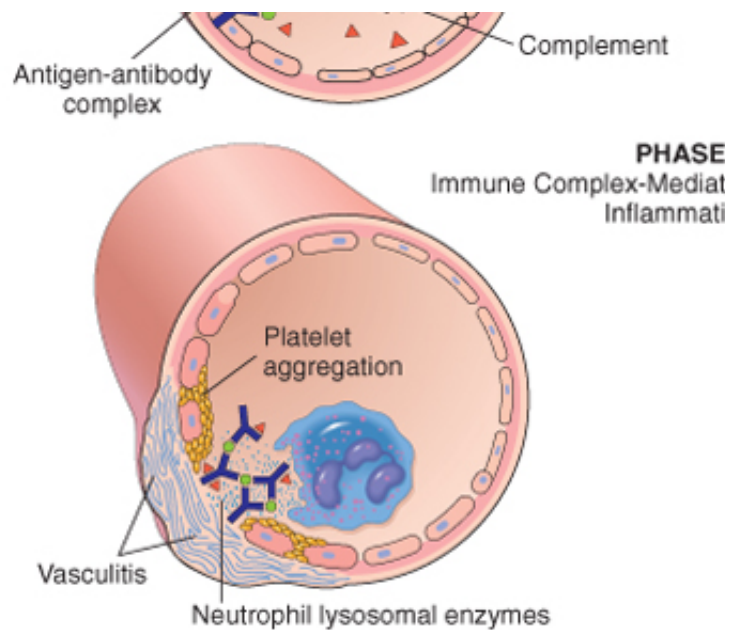
Polyarteritis nodosa	Hepatitis B virus antigen
Reactive arthritis	Bacterial antigens ( <i>Yersinia</i> )
Serum sickness	Various proteins, such as foreign serum protein (horse anti-thymocyte globulin)
Arthus reaction (experimental)	Various foreign proteins

### Systemic Immune Complex Disease

The pathogenesis of systemic immune complex disease can be divided into three phases: (1) formation of the immune complexes in the circulation and (2) deposition of the immune complexes in various tissues, thus initiating (3) an inflammatory reaction throughout the body (Fig. 5-12).

*Acute serum sickness* is the prototype of a systemic immune complex disease. It was first described when foreign serum was administered for passive immunization (e.g., horse serum containing antidipltheric serum). Infrequently (e.g., in patients injected with horse antithymocyte globulin for treatment of aplastic anemia as a therapeutic strategy). Approximately 5 days after a foreign protein is injected, specific antibodies are still present in the circulation to form antigen-antibody complexes. The complexes deposit in blood vessels and trigger the subsequent injurious inflammatory reaction. Several variables determine whether immune complexes cause deposition and disease. Perhaps foremost among these is the size of the complexes. Very large complexes (e.g., IgG Fc regions (typically formed in antibody excess)) are rapidly removed from the circulation by macrophages and are therefore usually harmless. The most pathogenic complexes are formed during antigen excess and are cleared less effectively by phagocytes, and therefore circulate longer. In addition, the charge and the hemodynamics of a given vascular bed all influence the tendency for deposition. Localization in the kidney is influenced by hemodynamic pressures associated with the filtration function of the glomerulus and the synovium. In the joint, complexes deposit within or outside the vessel wall, an increase in vascular permeability must also occur. In the skin, complexes bind to leukocytes and mast cells via Fc and C3b receptors and stimulate release of mediators of inflammation.





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Figure 5-12 Immune complex disease. The sequential phases in the induction of systemic immune complex-n

Once complexes are deposited in the tissue, the third phase, the inflammatory reaction, ensues. [after antigen administration), clinical features such as fever, urticaria, arthralgias, lymph node enlargement. Wherever immune complexes deposit, the tissue damage is similar. The immune complexes activate the release of biologically active fragments such as the anaphylatoxins (C3a and C5a), which are chemotactic for neutrophils and monocytes (Chapter 2). The complexes also bind to Fcγ receptors, activate these cells. Attempted phagocytosis of immune complexes by the leukocytes results in the release of proinflammatory substances, including prostaglandins, vasodilator peptides, and chemotactic substances capable of digesting basement membrane, collagen, elastin, and cartilage, and reactive-oxygen species. Immune complexes can also cause platelet aggregation and activate Hageman factor; both of these reactions initiate formation of microthrombi, which contribute to the tissue injury by producing local ischemia. The pathologic lesion is termed *vasculitis* if it occurs in blood vessels, *glomerulonephritis* if it occurs in the kidney, *arthritis* if it occurs in joints, and so on.

Predictably, the antibody classes that induce such lesions are complement-fixing antibodies (i.e., IgG and IgM). IgA can also induce tissue injury. Because IgA can activate complement by the alternative pathway, it can also induce tissue injury. During the active phase of the disease, consumption of complement may result in low levels. The role of complement- and Fc receptor-dependent inflammation in the pathogenesis of these lesions is supported by observations that experimental depletion of serum complement levels or knockout of Fc receptors results in less severe lesions, as does depletion of neutrophils.

### Morphology

The morphologic appearance of immune complex injury is dominated by acute necrosis, microthrombi, and superimposed ischemic necrosis accompanied by acute inflammation in affected organs. The necrotic vessel wall takes on a smudgy eosinophilic appearance called *fibrinoid*, caused by protein deposition (see Fig. 1-14, Chapter 1). Immune complexes can be deposited usually in the vascular wall; examples of such deposits in the kidney in lupus are shown in Figure 5-13. In some cases the lesions tend to resolve, especially when they were brought about by a self-limiting process (e.g., acute serum sickness and acute poststreptococcal glomerulonephritis [Chapter 2]). Immune complex disease develops when there is persistent antigenemia or repeated antigen exposure. This occurs in some human diseases, such as systemic lupus erythematosus (SLE). In SLE, the morphologic changes and other findings strongly implicate immune complex deposition as the cause, but the antigens are unknown.



## Local Immune Complex Disease

A model of local immune complex diseases is the *Arthus reaction*, an area of tissue necrosis and vasculitis. The reaction is produced experimentally by injecting an antigen into the skin of a preimmunized animal (antibodies against the antigen are already present in the circulation). Because of the initial antibodies, as the antigen diffuses into the vascular wall, these are precipitated at the site of injection and trigger a histologic appearance as in systemic immune complex disease. Arthus lesions evolve over a few days after injection, when the injection site develops visible edema with severe hemorrhage, occasionally

## T-Cell-Mediated (Type IV) Hypersensitivity

The occurrence and significance of T-lymphocyte-mediated tissue injury have been increasingly appreciated, and purifying T cells from patients' circulation and lesions have improved. This group of diseases includes many of the new, rationally designed biologic therapies for immune-mediated inflammatory diseases and abnormal T-cell reactions. Several autoimmune disorders, as well as pathologic reactions to environmental microbes, are now known to be caused by T cells (Table 5-5). Two types of T-cell reactions are clinically important: (1) *delayed-type hypersensitivity (DTH)*, initiated by CD4<sup>+</sup> T cells, and (2) *direct cell cytotoxicity* (Fig. 5-13). In DTH, T<sub>H</sub>1-type CD4<sup>+</sup> T cells secrete cytokines, leading to recruitment of other cells, especially effector cells of injury. In cell-mediated cytotoxicity, cytotoxic CD8<sup>+</sup> T cells are responsible for tissue

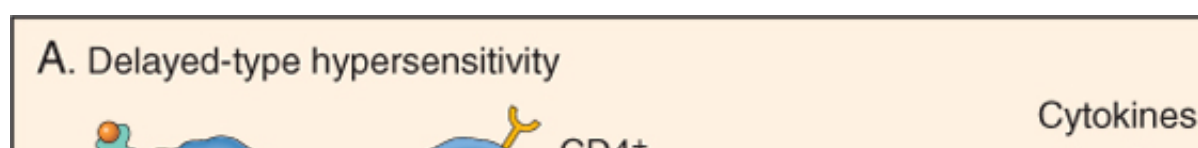
## Delayed-Type Hypersensitivity

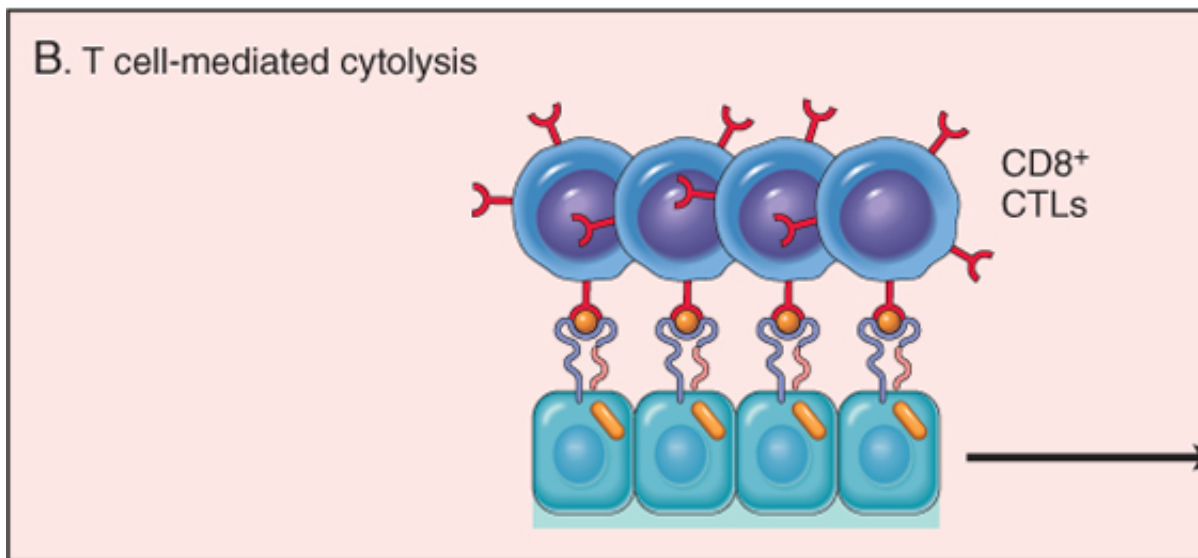
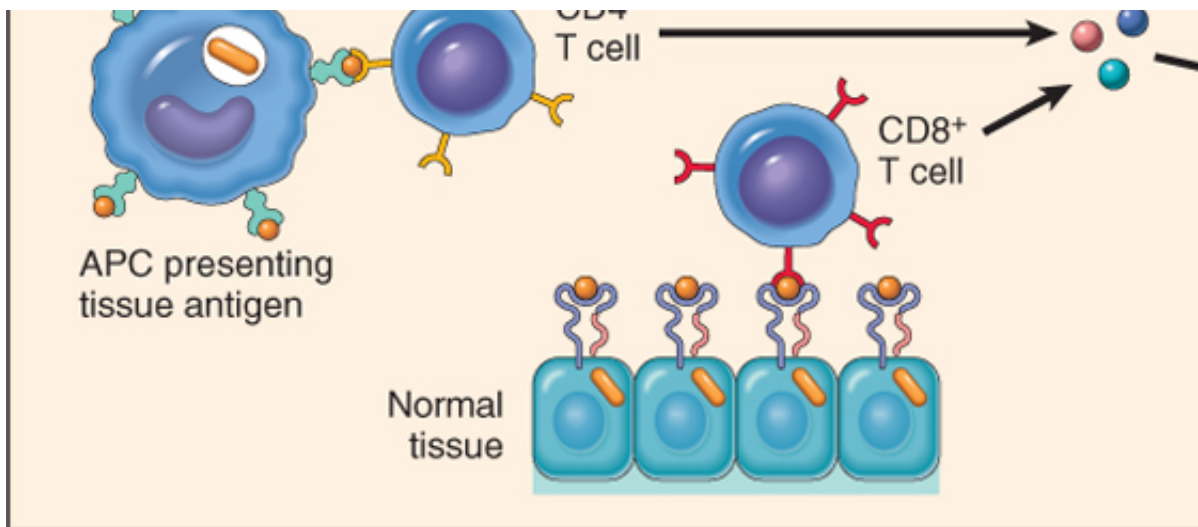
Table 5-5. Examples of T-Cell-Mediated (Type IV) Hypersensitivity

Disease	Specificity of Pathogenic T cells	Clinicopathology
Type 1 diabetes mellitus	Antigens of pancreatic islet $\beta$ cells (insulin, glutamic acid decarboxylase, others)	Insulinitis (chronic $\beta$ cells; diabetes)
Multiple sclerosis	Protein antigens in CNS myelin (myelin basic protein, proteolipid protein)	Demyelination in optic neuritis, paralysis, ocular
Rheumatoid arthritis	Unknown antigen in joint synovium (type II collagen?); role of antibodies?	Chronic arthritis with articular cartilage
Peripheral neuropathy; Guillain-Barré syndrome?	Protein antigens of peripheral nerve myelin	Neuritis, paralysis
Inflammatory bowel disease (Crohn's disease)	Unknown antigen; may be derived from intestinal microbes	Chronic inflammation; granulomas; fibrosis
Contact dermatitis	Environmental chemicals, e.g., poison ivy (pentadecylcatechol)	Dermatitis, with inflammation; chronic with persistent

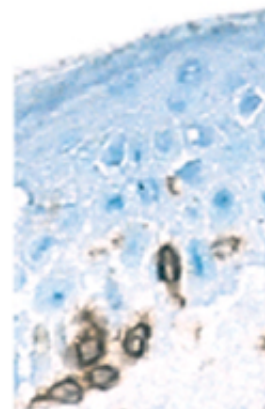
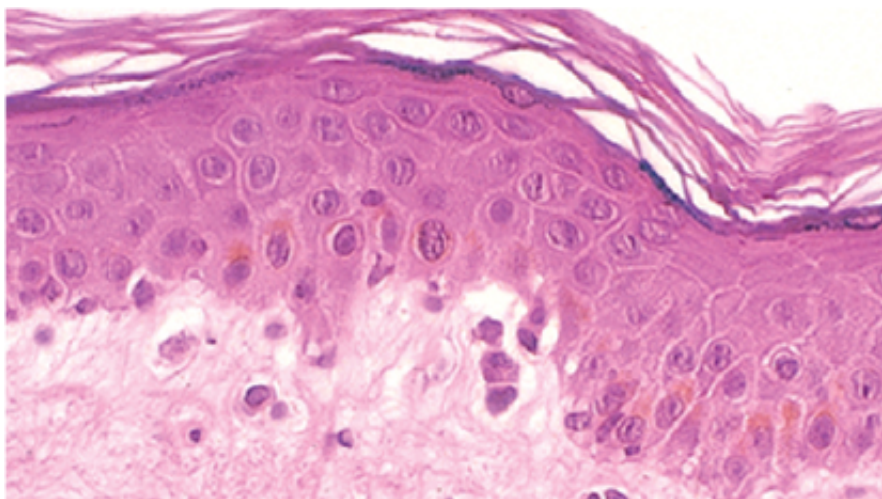
CNS, central nervous system.

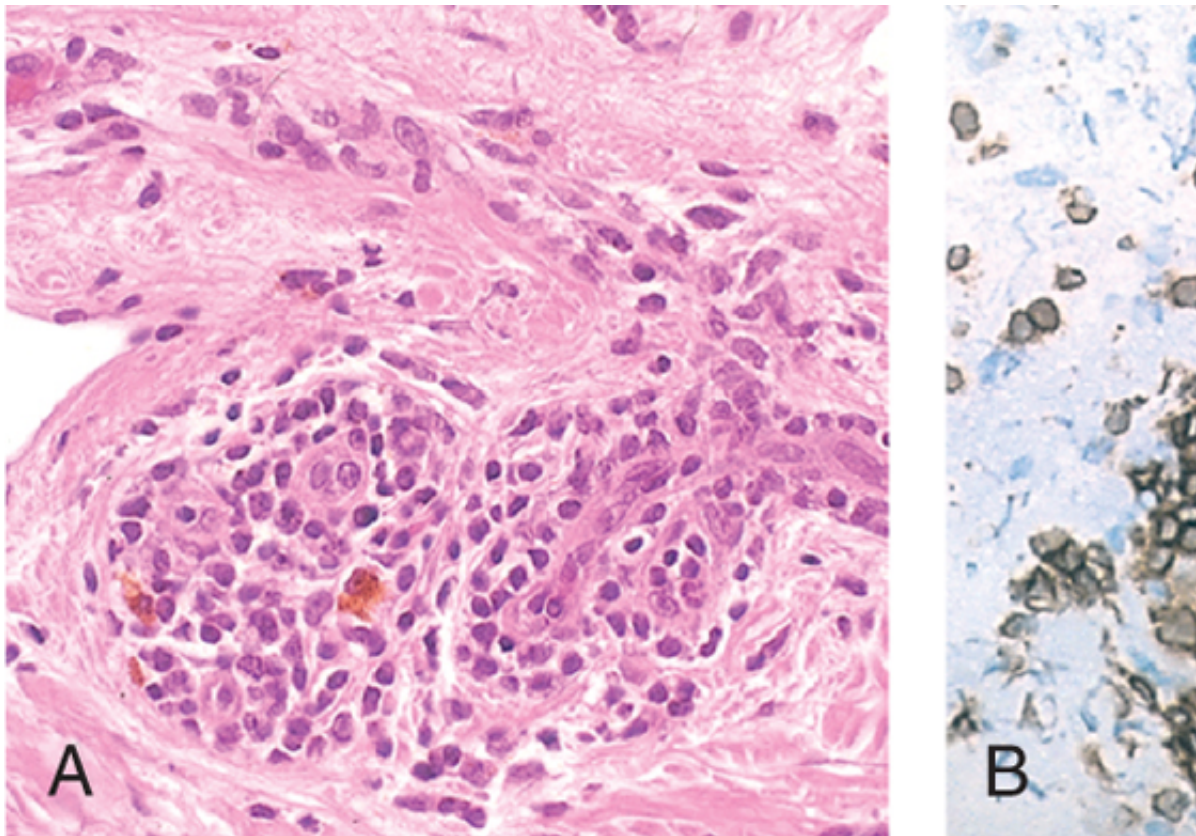
A classic example of DTH is the *tuberculin reaction*, elicited by antigen challenge in an individual previously sensitized by a previous infection (Chapter 13). Between 8 and 12 hours after intracutaneous injection of tuberculin (protein extract of *Mycobacterium tuberculosis* bacillus), a local area of erythema and induration appears, reaching a peak (typically 1-2 cm in diameter) at 24-48 hours (Fig. 5-14). The adjective, *delayed*, refers to the time course of the reaction and thereafter slowly subsiding. Histologically, the DTH reaction is characterized by infiltration ("cuffing") of CD4<sup>+</sup> helper T cells and macrophages (Fig. 5-14). Local secretion of cytokines by these cells leads to increased microvascular permeability, giving rise to dermal edema and fibrin deposition; this is the basis of the induration in these responses. The tuberculin response is used to screen populations for individuals with latent tuberculosis and therefore have circulating memory T cells specific for mycobacterial proteins. No CD4<sup>+</sup> T cells (e.g., resulting from HIV infection) may lead to a negative tuberculin response even





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 Figure 5-13 Mechanisms of T-cell-mediated (type IV) hypersensitivity reactions. **A**, In delayed-type hypersensitivity (cells) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leac  
 CTLs directly kill tissue cells. APC, antigen-presenting cell.



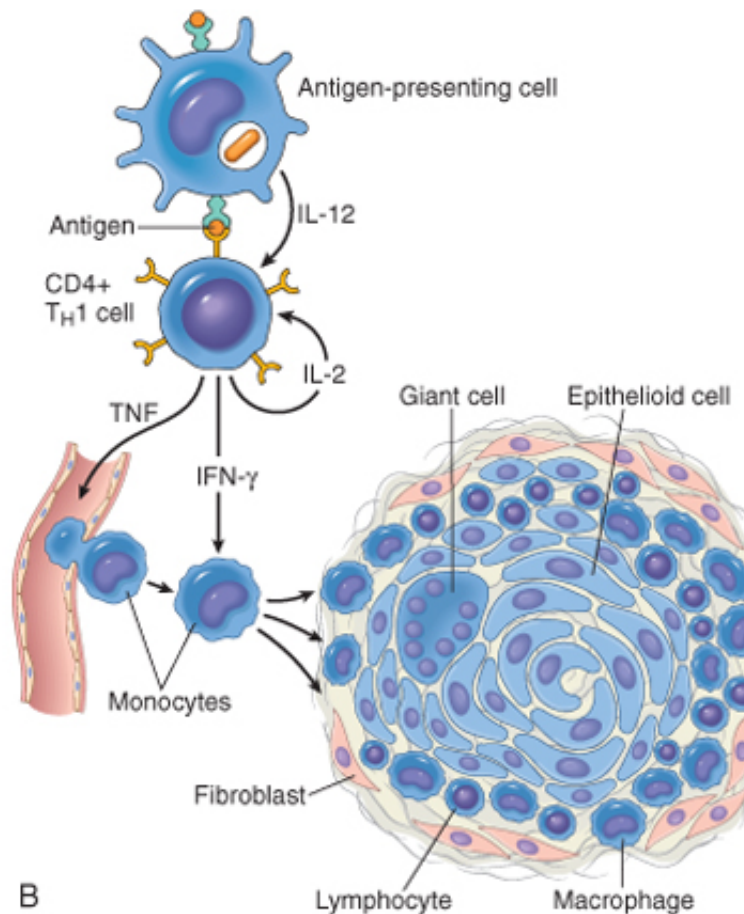
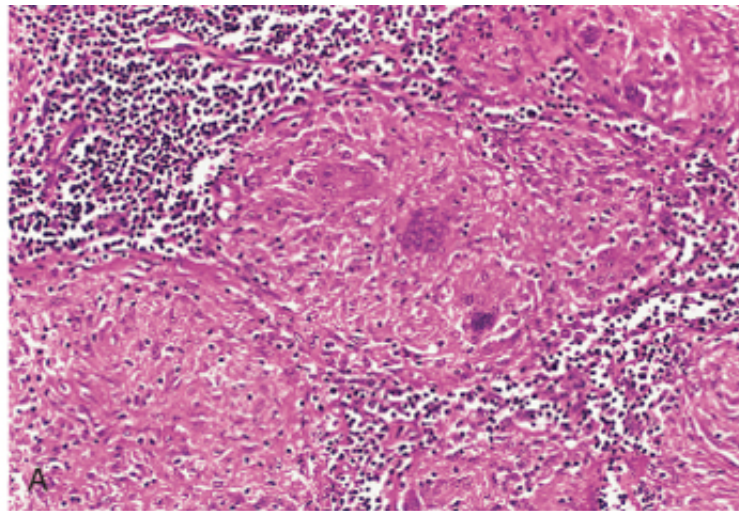


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 Figure 5-14 Delayed-type hypersensitivity reaction in the skin. **A**, Perivascular accumulation ("cuffing") of mononuclear cells (macrophages), with associated dermal edema and fibrin deposition. **B**, Immunoperoxidase staining reveals a predominantly CD4+ population of cells, positive with anti-CD4 antibodies. (**B**, Courtesy of Dr. Louis Picker, Department of Pathology, Oregon Health Sciences University)

The sequence of events in DTH, as exemplified by the tuberculin reaction, begins with the first exposure to the antigen and is essentially the same as the reactions of cell-mediated immunity (see Fig. 5-6). Naive CD4+ T cells recognize antigens of tubercle bacilli in association with class II MHC molecules on the surface of DCs (or macrophages) or mycobacterial antigens. This process leads to the generation of effector and memory CD4+ T cells. Memory cells remain in the circulation or tissues for years. Many variables may determine why some stimuli induce a DTH response and others do not. One of these is the activation of APCs by the engagement of Toll-like receptors by microbial components or by the cytokine *IL-12* by the APCs. *IL-12* acts on the responding T cells and drives their differentiation along the Th1 pathway. Interleukin-12, produced by NK cells and by the Th1 cells themselves, further promotes Th1 differentiation, providing a positive feedback loop. Upon subsequent exposure to the antigen (e.g., tuberculin), the previously generated Th1 effector and memory cells are activated by the antigen presented by local APCs. The Th1 cells secrete interferon- $\gamma$ , a macrophage-activating cytokine known and the major mediator of the DTH reaction. Activated macrophages exhibit enhanced phagocytic and microbicidal activity. They also secrete several polypeptide growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor  $\beta$  (TGF- $\beta$ ), which stimulate fibroblast proliferation and augment collagen synthesis, enhancing the ability of macrophages to eliminate offending agents; if the activation is sustained, macrophages also express more class II MHC molecules and costimulators, leading to augmented antigen presentation and more *IL-12*, thus stimulating more Th1 responses. Because of these multiple feedback loops, DTH is a self-amplifying process. If the offending agent is eliminated or the cycle is interrupted therapeutically, the reaction subsides.

Other cytokines produced by Th1 cells also play significant roles in the DTH reaction. *IL-2* causes increased vascular permeability and accumulation of cells at sites of DTH. *TNF* and *lymphotoxin* are cytokines that exert important effects on endothelial cells, causing local vasodilation and increased blood flow; (2) increased expression of adhesion molecules (integrins (Chapter 2), adhesion molecules that promote leukocyte attachment; and (3) secretion of proteolytic enzymes. These changes facilitate the recruitment of lymphocytes and monocytes to the site of DTH response.





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 Figure 5-15 Granulomatous inflammation. **A**, A section of a lymph node shows several granulomas, each made of macrophages and T cells, surrounded by lymphocytes. The granuloma in the center shows several multinucleated giant cells. **B**, The events that lead to granulomatous inflammation in type IV hypersensitivity reactions. Note the role played by T-cell-derived cytokines. (**A**, Courtesy of Dr. Trace Worrell, Southwestern Medical School, Dallas, Texas.)

Prolonged DTH reactions against persistent microbes or other stimuli may result in a special morphologic pattern called *granulomatous inflammation*. The initial perivascular CD4<sup>+</sup> T-cell infiltrate is progressively replaced by a dense infiltrate of macrophages and T cells, forming a granuloma.

*granulomatous inflammation*. The initial perivascular CD4<sup>+</sup> T-cell infiltrate is progressively replaced over weeks; these accumulated macrophages typically exhibit morphologic evidence of activation, that is, they are eosinophilic (denoted as *epithelioid cells*). The epithelioid cells occasionally fuse under the influence of IFN- $\gamma$  to form multinucleated *giant cells*. A microscopic aggregate of epithelioid cells, typically surrounded by a rim of fibroblasts and connective tissue, is called a *granuloma* (Fig. 5-15A). The process is essentially the same as that described for other DTH responses. In some cases, granulomas develop an enclosing rim of fibroblasts and connective tissue. Recognition of a granuloma is of diagnostic value in a limited number of conditions that can cause it (Chapter 2).

As mentioned earlier, the T cell-macrophage reaction that typifies DTH is also the central reaction in the mechanism of host defense against a variety of intracellular pathogens, including mycobacteria, fungi, and viruses. In these situations, protective cell-mediated immunity and damaging DTH may coexist. The same mechanisms are involved in rejection and tumor immunity. The critical role of CD4<sup>+</sup> T cells in protective, cell-mediated immunity is evident in the loss of CD4<sup>+</sup> cells in these patients results in a markedly impaired host response against intracellular pathogens such as *tuberculosis*. The bacteria are engulfed by macrophages but are not killed, and instead of granuloma formation, unactivated macrophages poorly adapted to deal with the invading microbe.

DTH reactions are the underlying basis of several diseases. *Contact dermatitis* is an example of a DTH reaction evoked by contact with pentadecylcatechol (also known as urushiol, the active component of poison ivy). Urushiol becomes antigenic by binding to a host protein. Exposure of a sensitized host elicits the reaction, contact dermatitis. The basic mechanism is similar to that described for tuberculin sensitivity. On re-exposure, CD4<sup>+</sup> T cells accumulate in the dermis and migrate toward the antigen within the epidermis. Here they release cytokines that kill keratinocytes, causing separation of these cells and formation of an intraepidermal vesicle. It has been suggested that autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and Crohn disease, are caused by T<sub>H</sub>1 reactions. Recent studies, mostly in mice, have implicated another CD4<sup>+</sup> T-cell subset, the "T<sub>H</sub>17" cells, in the pathogenesis of these diseases. One of the cytokines in this subset is IL-17, which is a potent inducer of inflammation. It may be that T<sub>H</sub>17 cells are implicated in the pathogenesis of autoimmune diseases, such as Crohn disease and multiple sclerosis.

### **T-Cell-Mediated Cytotoxicity**

#### **SUMMARY**

#### **Mechanisms of T-Cell-Mediated Hypersensitivity Reactions**

*Delayed-type hypersensitivity (DTH):* CD4<sup>+</sup> T cells are activated by exposure to an antigen and differentiate into T<sub>H</sub>1 effector cells. Subsequent exposure to the antigen results in the release of cytokines. IFN- $\gamma$  activates macrophages to produce substances that cause tissue damage, promote fibrosis, and TNF promotes inflammation. *T-cell-mediated cytotoxicity:* CD8<sup>+</sup> T lymphocytes (CTLs) specific for an antigen recognize cells expressing the antigen. CD8<sup>+</sup> T cells also secrete IFN- $\gamma$ .

In this form of T-cell-mediated hypersensitivity, CD8<sup>+</sup> CTLs kill antigen-bearing target cells. As described in Chapter 1, CD8<sup>+</sup> T cells bind to intracellular peptide antigens and present the peptides to CD8<sup>+</sup> T lymphocytes, stimulating them to become effector cells called CTLs. CTLs play a critical role in resistance to virus infections and some tumors. The killing mechanism of CTLs is dependent on the perforin-granzyme system. Perforin and granzymes are stored in the granules of CTLs. When CTLs engage their targets (cells bearing the appropriate class I MHC-bound peptides), perforin is released and forms pores in the target cell membrane. These pores promote the entry of granzymes, which are proteases that specifically cleave and kill the target cells. These enzymes induce apoptotic death of the target cells (Chapter 1). CTLs play an important role in the rejection of transplants and may contribute to many immunologic diseases, such as type 1 diabetes (in which the pancreatic islets are destroyed by an autoimmune T-cell reaction).

Having described the basic mechanisms of pathologic immune reactions, we proceed to a discussion of two types of reactions of great clinical importance: transplant rejection and autoimmunity.









## REJECTION OF TRANSPLANTS

The major barrier to transplantation of organs from one individual to another of the same species is the rejection of the transplanted tissue. Rejection is a complex phenomenon involving both cell- and antibody-mediated immunity directed against histocompatibility molecules on the foreign graft. The key to successful transplantation is the development of therapies that prevent or minimize rejection. Below we discuss how grafts are recognized as foreign.

### Immune Recognition of Allografts

Rejection of allografts is a response to MHC molecules, which are so polymorphic that no two individuals express exactly the same set of MHC molecules (except, of course, for identical twins). Therefore, the host immune system recognizes and responds to the MHC molecules on the graft (Fig. 5-16).

**Direct recognition.** Host T cells directly recognize the allogeneic (foreign) MHC molecules. This type of recognition of foreign MHC seems to violate the rule of MHC restriction, which states that T cells are educated to recognize foreign antigens displayed by only that individual's MHC molecules. However, donor MHC molecules (with any bound peptides) structurally mimic self-MHC and foreign peptide, and MHC is essentially an immunologic cross-reaction. Because DCs in the graft express high levels of costimulatory molecules, they are the most likely APCs in direct recognition. Host CD4<sup>+</sup> helper T cells drive cytokine production by recognition of donor class II MHC (HLA-D) molecules and drive CD8<sup>+</sup> cytotoxic T cells to recognize class I MHC (HLA-A, -B) and differentiate into CTLs, which kill the cells in the graft. Alternatively, host CD4<sup>+</sup> T cells recognize donor MHC molecules after these molecules are picked up by host APCs. This is similar to the physiologic processing and presentation of other foreign antigens. Direct recognition mainly activates DTH pathways; CTLs that develop by indirect recognition cannot. The indirect pathway is also involved in the production of antibodies against graft alloantigens. These antibodies are picked up by host B cells, and peptides are presented to helper T cells, which then stimulate B cells to produce more antibodies.

### Effector Mechanisms of Graft Rejection

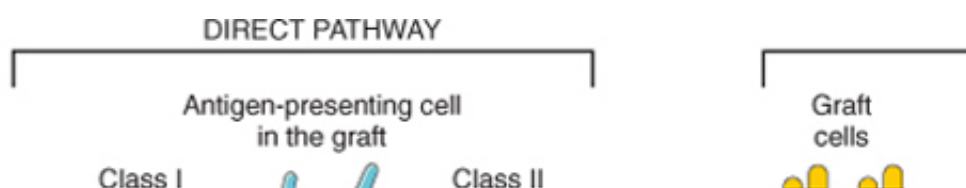
Both T cells and antibodies reactive with the graft are involved in the rejection of most solid-organ transplants.

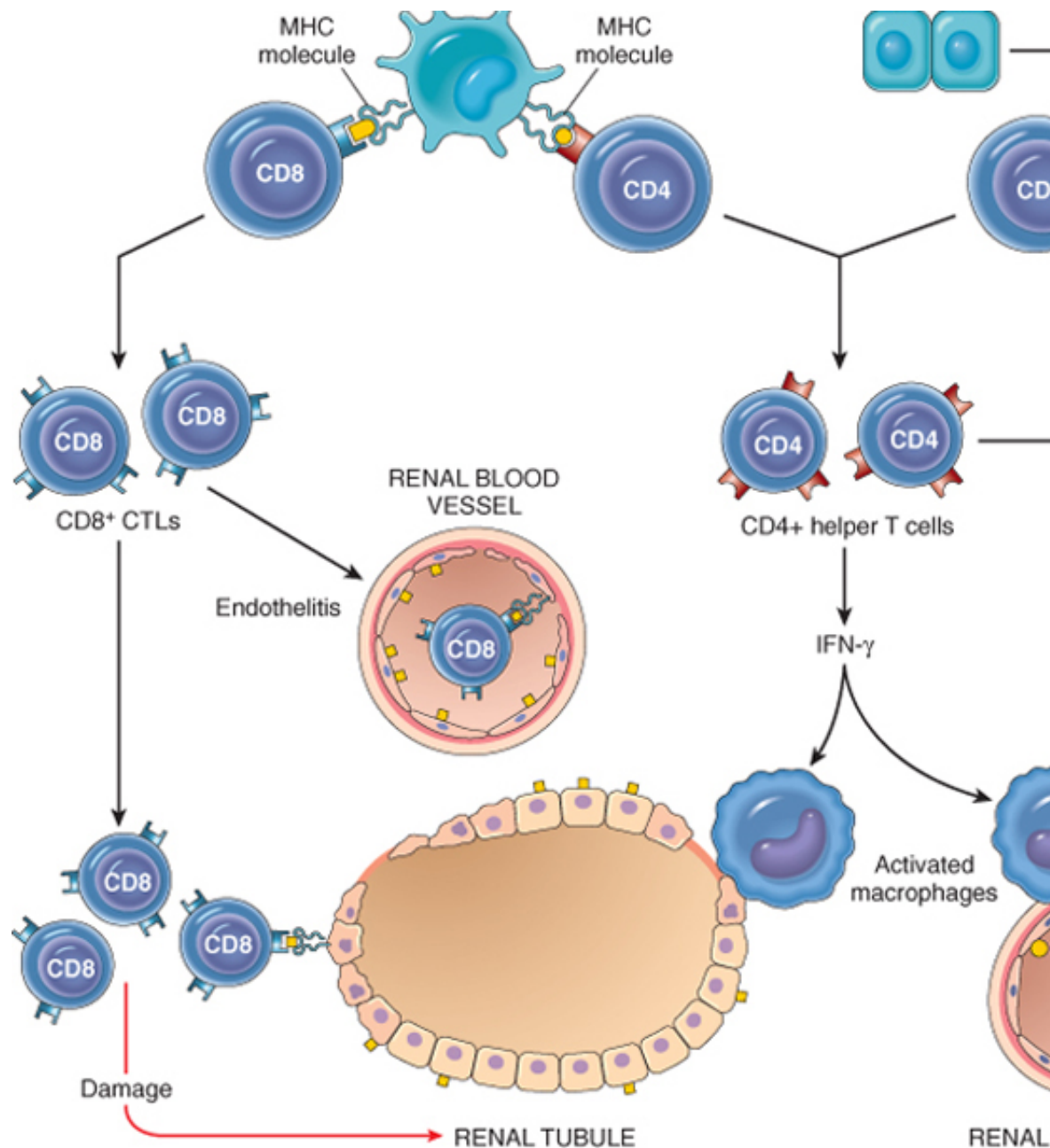
#### T-Cell-Mediated Rejection

CTLs kill cells in the grafted tissue, causing parenchymal and, perhaps more importantly, endothelial damage (causing graft ischemia). Cytokine-secreting CD4<sup>+</sup> T cells trigger DTH reactions, with increased vascular permeability and recruitment of mononuclear cells (lymphocytes and macrophages). Activated macrophages can injure graft cells, and the resulting tissue ischemia also results in tissue ischemia, which contributes to graft destruction.

#### Antibody-Mediated Rejection

Although T cells are of paramount importance in allograft rejection, antibodies also mediate some rejection. Antibodies against graft MHC molecules and other alloantigens bind to the graft endothelium and cause injury by complement activation and recruitment of leukocytes. Superimposed on the immunologic vascular injury is complement activation and coagulation (caused by complement activation), adding further ischemic insult to the injury. Histologically, the vasculitis of antibody-mediated hypersensitivity, described earlier. Local deposition of complement C4d is now widely used to detect humoral (antibody-mediated) rejection of kidney allografts.





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Figure 5-16 Recognition and rejection of organ allografts. In the direct pathway, donor class I and class II MHC antigens (along with costimulators, not shown) are recognized by host CD8<sup>+</sup> cytotoxic T cells and CD4<sup>+</sup> helper T cells, which release cytokines (e.g., IFN-γ), which induce tissue damage by a local delayed-hypersensitivity reaction. CD8<sup>+</sup> T cells release cytotoxic granules that kill graft cells. In the indirect pathway, graft antigens are displayed by host APCs and activate CD4<sup>+</sup> T cells, which induce a hypersensitivity reaction and stimulate B lymphocytes to produce antibodies.

**Hyperacute rejection** is a special form of rejection occurring in the setting where *preformed antibodies* circulate in the host before transplant. This may occur in multiparous women who have anti-HLA encountered during pregnancy, or in individuals exposed to foreign HLA (on platelets or leukocytes). Obviously, such antibodies may also be present in a host who has previously rejected an organ transplant. Hyperacute rejection results in immediate rejection (within minutes to hours) because the circulating antibodies rapidly bind to the graft, with subsequent complement activation and vascular thrombosis. Note that with the current use of preformed anti-HLA antibodies and cross-matching (testing recipients for the presence of anti-lymphocytes), hyperacute rejection occurs in less than 0.4% of transplants.

## Morphology

On the basis of the mechanisms involved, the resulting morphology, and the temporal course, rejection reactions have been classified as hyperacute, acute, and chronic (Fig. 5-17). The patterns of these reactions are described in the context of renal transplants; however, similar changes are seen in any other vascularized organ transplant.

**Hyperacute Rejection.** Hyperacute rejection occurs within minutes to a few hours in a sensitized host and is typically recognized by the surgeon just after the vascular anastomosis is completed. In contrast to a nonrejecting kidney graft that regains a normal pink color and promptly excretes urine, a hyperacutely rejecting kidney rapidly becomes cyanotic, may excrete only a few drops of bloody fluid. The histology is characterized by widespread arteriolitis, vessel thrombosis, and ischemic necrosis, all resulting from the binding of donor antibodies to graft endothelium. Virtually all arterioles and arteries exhibit characteristic acute fibrin deposition in the walls, with narrowing or complete occlusion of the lumens by precipitated fibrin and leukocyte infiltration (Fig. 5-17A).

**Acute Rejection.** Acute rejection may occur within days to weeks of transplantation in a nonimmunosuppressed host or may appear months or even years later, even in the presence of immunosuppression. Acute rejection is caused by both cellular and humoral immune responses; in any one patient one or the other may predominate. Histologically, cellular rejection is characterized by mononuclear cell infiltration with associated edema and parenchymal injury, whereas humoral rejection is associated with vasculitis.

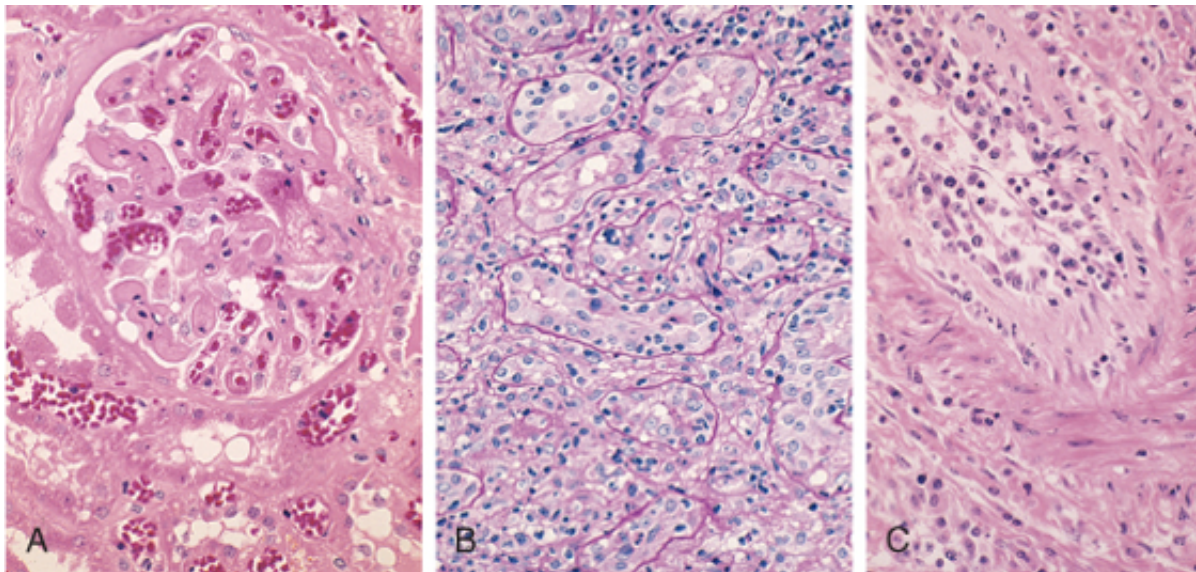
**Acute cellular rejection** is most commonly seen within the first months after transplantation and is usually accompanied by clinical signs of renal failure. Histologically, there is usually extensive interstitial CD8+ T-cell infiltration with edema and mild interstitial hemorrhage (see Fig. 5-17B). Peritubular capillaries contain large numbers of mononuclear cells, which may also cause focal tubular necrosis. In addition to tubular injury, CD8+ T cells may also injure the endothelium, causing an endotheliitis. Cyclosporine® (a widely used immunosuppressive agent) causes so-called arteriolar hyaline deposits. Renal biopsy is used to distinguish rejection from infection. Accurate recognition of cellular rejection is important, because in the absence of accurate diagnosis patients typically respond promptly to increased immunosuppressive therapy.

**Acute humoral rejection** (rejection vasculitis) caused by antidonor antibodies may lead to graft rejection. The histologic lesions may take the form of necrotizing vasculitis with neutrophilic infiltration; deposition of antibody, complement, and fibrin; and thrombosis of the vessel lumen associated with ischemic necrosis of the renal parenchyma. In many cases, the vasculitis is characterized by marked thickening of the intima by proliferating fibroblasts, myocytes, and macrophages (see Fig. 5-17C). The resultant narrowing of the arterioles may cause cortical atrophy. The proliferative vascular lesions mimic arteriosclerotic thickening caused by cytokines that stimulate proliferation of vascular smooth muscle cells.

**Chronic Rejection.** Patients with chronic rejection present clinically late after transplantation (months to years) with a progressive rise in serum creatinine levels (an index of renal dysfunction). Chronic rejection is dominated by vascular changes, interstitial fibrosis, and atrophy of the renal parenchyma; there are typically only mild or even no ongoing cellular changes. The changes occur predominantly in the arteries and arterioles, which exhibit intimal smooth muscle proliferation and extracellular matrix synthesis (Fig. 5-20D). These lesions ultimately impair renal perfusion and result in renal ischemia manifested by loss of glomeruli and tubular atrophy. The vascular lesion may be caused by cytokines released by activated T cells of the vascular wall, and it may be the end stage of the proliferative arteritis of acute rejection. Chronic rejection does not respond to standard immunosuppression regimens.







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Figure 5-17 Morphologic patterns of graft rejection. **A**, Hyperacute rejection of a kidney allograft showing endothelial glomerular changes. **B**, Acute cellular rejection of a kidney allograft with inflammatory cells in the interstitium and between glomeruli. **C**, Rejection vasculitis of a kidney allograft (rejection vasculitis) with inflammatory cells and proliferating smooth muscle cells in the vessel wall. The arterial lumen is replaced by an accumulation of smooth muscle cells and inflammatory cells. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School.

## SUMMARY

### Recognition and Rejection of Organ Transplants (Allografts)

The graft rejection response is initiated mainly by host T cells that recognize antigens of the graft, either directly (on APCs in the graft) or indirectly (after uptake of graft antigens by APCs). Types and mechanisms of rejection:

1. *Hyperacute rejection*. Preformed antidonor antibodies bind to graft endothelium after transplantation, leading to thrombosis, ischemic damage, and rejection.
2. *Acute cellular rejection*. T cells destroy graft parenchyma by cytotoxicity.
3. *Acute vascular rejection*. T cells and antibodies damage graft vasculature.
4. *Chronic rejection*. Dominated by arteriosclerosis, this type is probably mediated by secretion of cytokines that induce proliferation of vascular smooth muscle cells with parenchymal fibrosis.

### Methods of Improving Graft Survival

Because HLA molecules are the major targets in transplant rejection, better matching of the donor and recipient is essential. The benefits of HLA matching are most dramatic in living related donor kidney transplants, and solid organ transplants. However, as drugs for immunosuppression have improved, HLA matching is not essential in heart, lung, and liver transplantation; in these cases, the recipient often needs a transplant urgent anatomic compatibility, are of greater practical importance.

Immunosuppression of the recipient is a practical necessity in all organ transplantation except in the case of autotransplantation. Drugs such as cyclosporine<sup>®</sup>, the related FK506, mofetil mycophenolate (MMF), rapamycin, azathioprine, and monoclonal antibodies (e.g., monoclonal anti-CD3) are used. Cyclosporine<sup>®</sup> and FK506 act by inhibiting transcription of cytokine genes, in particular, the gene for IL-2. Although immunosuppression makes transplantation of many organs feasible, there is still a price to be paid. Global immunosuppression results in increased susceptibility to viral, and other infections. These patients are also at increased risk for developing Epstein-Barr virus-induced lymphomas, papillomavirus-induced squamous cell carcinomas, and Kaposi sarcoma (KS). To circumvent the

much effort is devoted to inducing donor-specific tolerance in host T cells. One strategy being pursued is to provide the recipient with agents that interrupt the interaction between the B7 molecules on the DCs of the graft with the CD28 and CTLA-4 receptors on the T cells. This can interrupt the second signal for T-cell activation and either induce apoptosis or render the T cells functionally anergic.

## Transplantation of Hematopoietic Cells

Bone marrow transplantation is increasingly used as therapy for hematopoietic and some nonhematopoietic diseases, and certain immune deficiency states. Hematopoietic stem cells are usually obtained from the donor and are harvested from peripheral blood after mobilization by administration of hematopoietic growth factors and/or irradiation to destroy malignant cells (e.g., in leukemia) and to create a graft bed; then, stem cell transplantation seems to be mediated by some combination of host T cells and donor T cells. *Two major problems complicate this form of transplantation: graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) effect.*

GVHD occurs when immunologically competent T cells (or their precursors) are transplanted into a recipient who is immunologically compromised. Although GVHD happens most commonly in the setting of allogeneic bone marrow transplantation (usually involving minor histocompatibility mismatches between donor and recipient), it may also occur after transfusion of nonirradiated blood. When a recipient receives allogeneic bone marrow cells, the host cannot reject the graft, but T cells present recipient's tissue as "foreign" and react against it. This results in the activation of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, leading to DTH and CTL responses.

*Acute GVHD* (occurring days to weeks after transplant) *causes epithelial cell necrosis in the skin, liver, and gut.* Destruction of small bile ducts gives rise to jaundice, and mucosal ulceration of the gastrointestinal tract. Cutaneous involvement is manifested by a generalized rash. *Chronic GVHD* may follow the acute form and is more insidious. These patients develop skin lesions resembling those of systemic sclerosis (dissecting collagen disease), mimicking other autoimmune disorders.

GVHD is a potentially lethal complication that can be minimized but not eliminated by HLA matching. Donor T cells can be depleted before marrow transplant. This protocol has proved to be a reduction in GVHD, but the incidence of graft failure and the recurrence of leukemia increase. It seems that donor T cells mediate GVHD but also are required for the efficient engraftment of the transplanted bone marrow cells (so-called *graft-versus-leukemia* effect). *Immune deficiencies*, often of prolonged duration, are common after marrow transplants. Among the many reasons for this are the slow reconstitution of the host immune system, the destruction or suppression of the host immune system to allow the graft to take, and an inability to fully regenerate all the components of the immune system. The consequence of the immune deficiency is that recipients are susceptible to a variety of infections, including cytomegalovirus (CMV) and EBV infections.





## AUTOIMMUNE DISEASES

Table 5-6. Autoimmune Diseases

Organ-Specific	Systemic
Hashimoto thyroiditis	Systemic lupus er
Autoimmune hemolytic anemia	Rheumatoid arthri
Autoimmune atrophic gastritis of pernicious anemia	Sjögren syndrome
Multiple sclerosis	Reiter syndrome
Autoimmune orchitis	Inflammatory myo
Goodpasture syndrome	Systemic sclerosis
Autoimmune thrombocytopenia	Polyarteritis nodo
Insulin-dependent diabetes mellitus	
Myasthenia gravis	
Graves' disease	
Primary biliary cirrhosis*	
Autoimmune (chronic active) hepatitis*	
Ulcerative colitis	

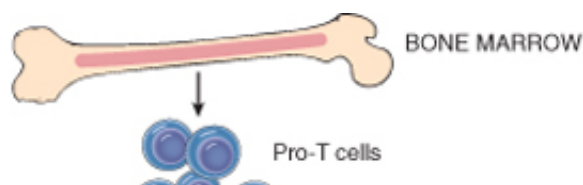
\*The evidence supporting an autoimmune basis of these disorders is not strong.

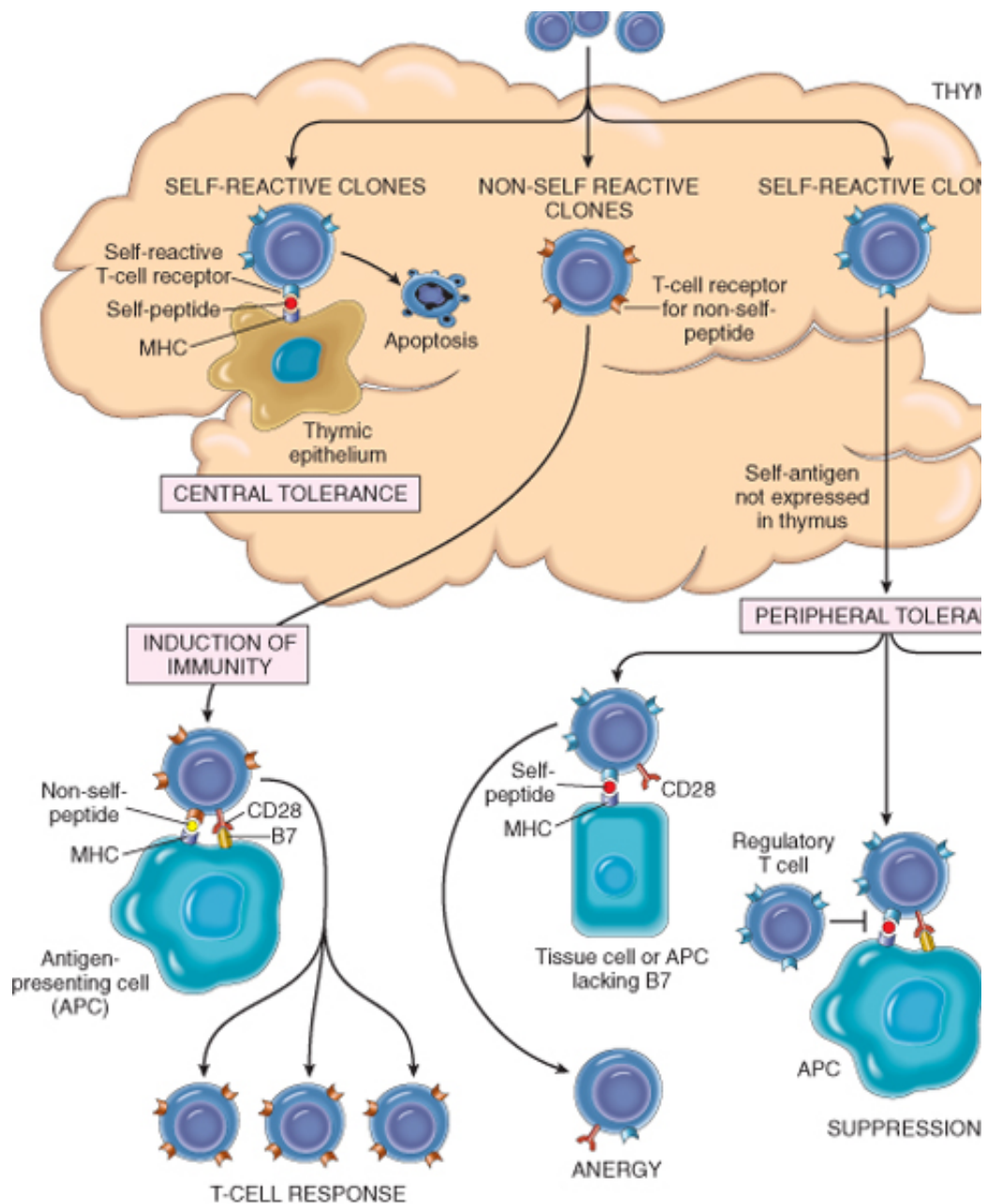
The evidence is compelling that an immune reaction to *self-antigens* (i.e., *autoimmunity*) is the cause of many of the entities have been attributed to this process (Table 5-6). However, in many of these diseases an important caveat is that the simple presence of autoreactive antibodies or T cells does *not* equate with disease. Low-affinity antibodies and T cells reactive with self-antigens can be readily demonstrated in most individuals. Presumably, these antibodies and T cells are not pathogenic and are of little consequence. Moreover, self-antigens are frequently generated following other forms of injury (e.g., ischemia) and may even be the products of tissue breakdown. The evidence that the diseases listed in Table 5-6 are indeed the result of an autoimmune reaction is more persuasive for some than for others. Thus, the presence of a multiplicity of autoantibodies accounts for the manifestations of SLE. Moreover, these autoantibodies can be identified within lesions by immunofluorescent techniques. In many other disorders, an autoimmune etiology is suspected but is unproven. Indeed, in some cases of autoimmunity the response may be directed against an exogenous antigen, such as a microbial product. For example, the vasculitis in many cases of polyarteritis nodosa.

Presumed autoimmune diseases range from those in which specific immune responses are directed against a single antigen and result in localized tissue damage, to multisystem diseases characterized by lesions in many organs. In the systemic diseases, autoantibodies or cell-mediated reactions against numerous self-antigens are involved. In the systemic diseases, the lesions involve connective tissue and blood vessels of the various organs involved. Thus, even though the system of defense is directed against constituents of connective tissue or blood vessels, the diseases are often referred to as "connective tissue disorders."

It is obvious that autoimmunity implies loss of self-tolerance, and the question arises as to how this loss occurs. In the pathogenesis of autoimmunity, it is important to first familiarize ourselves with the mechanisms of immunological tolerance.

### Immunological Tolerance





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Figure 5-18 The principal mechanisms of central and peripheral self-tolerance in

Immunological tolerance is unresponsiveness to an antigen that is induced by exposure of specific antigens. Central tolerance refers to a lack of immune responsiveness to one's own tissue antigens. During the generation of T and B lymphocytes, it is not surprising that receptors are produced that can recognize self-antigens. Since not all self-antigens can be concealed from the immune system, there must be means of eliminating or controlling self-reactive lymphocytes. These mechanisms work in concert to select against self-reactivity and to thus prevent immune reactions. These mechanisms are broadly divided into two groups: central tolerance and peripheral tolerance (Fig. 5-18).

**Central tolerance.** This refers to deletion of self-reactive T and B lymphocytes during their development (i.e., in the thymus for T cells and in the bone marrow for B cells). Many autologous (self) peptides are presented by MHC molecules to T-cell receptors. Self-reactive T cells are deleted by apoptosis.



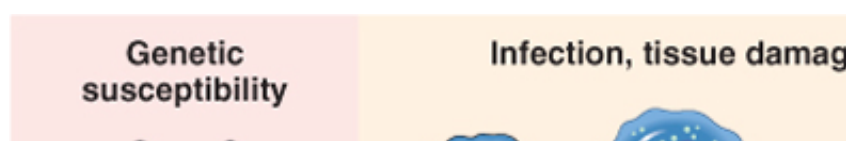
presented by thymic APCs in association with self-MHC. Any developing T cell that expresses a receptor that is negatively selected (deleted by apoptosis), and the resulting peripheral T-cell pool is therefore self-tolerant (Fig. 5-18). An exciting recent advance has been the identification of putative transcription factors that are apparently peripheral tissue antigens in the thymus. One such factor is called the autoimmune regulator (*AIRE*). Mutations in the *AIRE* gene are responsible for an autoimmune polyendocrine syndrome in which T cells undergo deletion, presumably because these self-antigens are not expressed in the thymus. Some T cells in the thymus are not killed but differentiate into regulatory T cells, which are described below. Immature B cells that recognize, with high affinity, self-antigens in the bone marrow may also be deleted, or cells may not be deleted but may undergo a second round of rearrangement of antigen receptor genes that are no longer self-reactive (a process called "receptor editing"). Unfortunately, the process of deletion of self-reactive lymphocytes is far from perfect. Many T cells in the thymus, and hence T cells bearing receptors for such autoantigens escape into the peripheral T-cell system as well, and B cells that bear receptors for a variety of self-antigens, including those found in healthy individuals, also escape. *Peripheral tolerance.* Self-reactive T cells that escape negative selection wreak havoc unless they are deleted or effectively muzzled. Several mechanisms in the periphery for deleting or inactivating potentially autoreactive T cells have been identified:

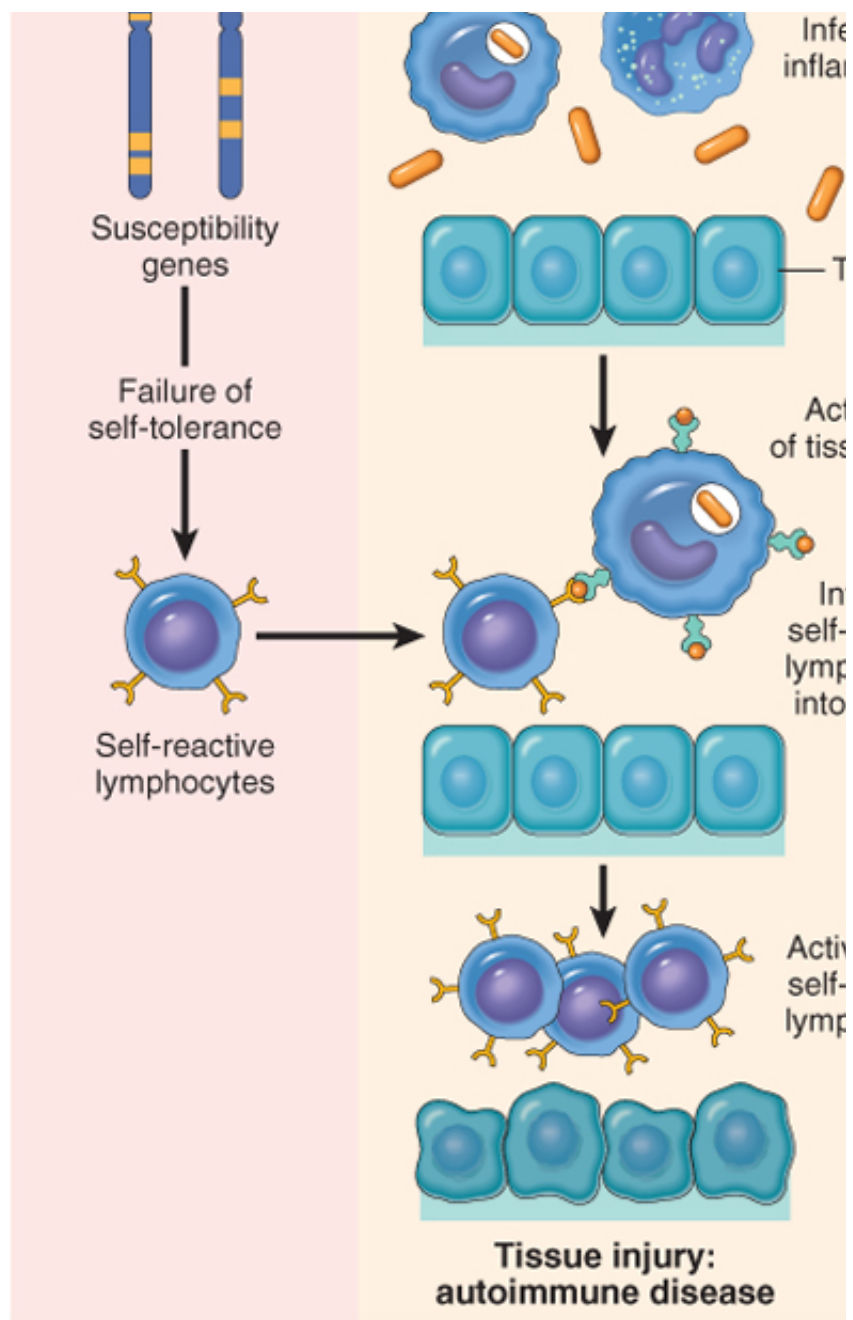
**Anergy:** This refers to functional inactivation (rather than death) of lymphocytes under certain conditions. Recall that activation of T cells requires two signals: recognition of antigen by the T-cell receptor (TCR) in association with MHC molecules on APCs, and a set of second costimulatory signals (e.g., via B7 molecules). If the second costimulatory signals are not delivered, or if an inhibitory receptor on the T cell (e.g., CTLA-4) is engaged when the cell encounters self-antigen, the T cell becomes anergic (see Fig. 5-21). Because costimulatory molecules are not strongly expressed on most cells in the periphery, autoreactive T cells and self-antigens in tissues may result in anergy. B cells can also become anergic if they encounter self-antigen in the absence of specific helper T cells. **Suppression by regulatory T cells:** Some self-reactive T cells may be actively suppressed by *regulatory T cells*. The best-defined population of these cells is the CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cell, which expresses a specific chain of the receptor for IL-2, and require IL-2 for their generation and survival. They also express a transcription factor called FoxP3, and this one protein seems to be both necessary and sufficient for their suppressive function. Mutations in the *FOXP3* gene are responsible for a systemic autoimmune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), which is associated with severe autoimmune diseases. The probable mechanism by which regulatory T cells control immune responses is through the secretion of cytokines (e.g., IL-10 and TGF- $\beta$ ), which can dampen a variety of T-cell responses. **Fas and Fas ligand:** Another mechanism of peripheral tolerance involves apoptosis of mature lymphocytes as a result of repeated stimulation by antigens in vitro undergo apoptosis. One mechanism involves the engagement of a receptor (a member of the TNF receptor family) being engaged by its ligand coexpressed on the same cell. This mechanism is important for the deletion of self-reactive B cells by Fas ligand expressed on helper T cells. **Self-tolerance is illustrated by the discovery that mutations in the *FAS* gene are responsible for a severe autoimmune disease called the autoimmune lymphoproliferative syndrome, characterized by lymphadenopathy and autoantibodies including anti-DNA. Defects in Fas and Fas ligand are also the cause of similar auto-**

## Mechanisms of Autoimmunity

Now that we have summarized the principal mechanisms of self-tolerance, we can ask how these mechanisms can fail and rise to pathologic autoimmunity. Unfortunately, there are no simple answers to this question, and the causes of most human autoimmune diseases are complex. We referred above to mutations that compromise the mechanisms of self-tolerance and cause pathologic autoimmunity. These single-gene mutations are extremely informative, and they have helped to define the significance of the various pathways of self-tolerance. The diseases caused by such mutations are rare, and the mechanisms of self-tolerance and the development of autoimmunity are probably related to the genes and changes in tissues, often induced by infections or injury, that alter the display and recognition of self-antigens.

The breakdown of self-tolerance and the development of autoimmunity are probably related to the genes and changes in tissues, often induced by infections or injury, that alter the display and recognition of self-antigens.





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 Figure 5-19 Pathogenesis of autoimmunity. Autoimmunity arises from many causes, including the inheritance of susceptibility genes, a failure of self-tolerance, and environmental triggers (inflammation, other inflammatory stimuli) that promote lymphocyte entry into tissues and tissue injury.

### Genetic Factors in Autoimmunity

There is abundant evidence that susceptibility genes play an important role in the development of

Autoimmune diseases have a tendency to run in families, and there is a greater incidence of autoimmune diseases in dizygotic twins. Several autoimmune diseases are linked with the *HLA locus*, especially c... frequency of a disease in an individual with a particular HLA allele, compared to individuals... the *relative risk* (Table 5-7). The relative risk ranges from 3-4 for rheumatoid arthritis and *H...*

ankylosing spondylitis and *HLA-B27*. However, the role of MHC genes in autoimmunity is still unclear. MHC molecules do not distinguish between self and foreign peptide antigens. It should also be noted that a susceptibility-related MHC allele never develops any disease, and, conversely, individuals without a particular MHC allele can develop the disease. Expression of a particular MHC gene is therefore but one variable in the development of autoimmunity. Genome-wide linkage analyses are revealing many genetic loci that are associated with autoimmune diseases. Some of these loci seem to be associated with several diseases, suggesting that there are common mechanisms of self-tolerance and immune regulation. Other loci are disease specific and may be related to the display of particular self-antigens. Despite enormous interest in this area, so far most of the genetic loci are on the major histocompatibility complex segments, and the actual genes have not been identified with certainty. Two genetic polymorphisms are quite strongly associated with certain autoimmune diseases. One, called *PTPN22*, encodes a protein tyrosine phosphatase, and certain variants are associated with rheumatoid arthritis and several other autoimmune diseases. Another, called *NOD2*, encodes an intracellular receptor for microbial peptides, and certain variants or mutants of this gene are associated with Crohn's disease in some populations. How these genes contribute to autoimmunity is still unclear.

**Table 5-7. Association of HLA with Disease**

Disease	HLA Allele	Relative Risk (approximate)
Ankylosing spondylitis	<i>B27</i>	10-100
Postgonococcal arthritis	<i>B27</i>	10-100
Acute anterior uveitis	<i>B27</i>	10-100
Rheumatoid arthritis	<i>DR4</i>	3-10
Autoimmune hepatitis	<i>DR3</i>	3-10
Primary Sjögren syndrome	<i>DR3</i>	3-10
Type 1 diabetes mellitus	<i>DR3</i>	3-10
	<i>DR4</i>	3-10
	<i>DR3/DR4</i>	10-100
21-Hydroxylase deficiency	<i>Bw47</i>	10-100

### **Role of Infections and Tissue Injury**

A variety of microbes, including bacteria, mycoplasmas, and viruses, have been implicated as triggers of autoimmune reactions by several mechanisms:

Viruses and other microbes, particularly certain bacteria such as streptococci and *Klebsiella*, can share epitopes with self-antigens, such that responses to the microbial antigen may attack self-tissue. This is called *molecular mimicry*. It is the probable cause of a few diseases, the best example being rheumatic fever, in which the immune response against streptococci cross-reacts with cardiac antigens. It is not known if more self-antigens are involved in other autoimmune diseases. Microbial infections with resultant tissue necrosis and inflammation can release self-antigens from dead cells, thus favoring a breakdown of T-cell anergy and subsequent autoimmunity. Tissue injury caused by infections and other triggers can also alter the presentation of tissue antigens by MHC molecules on resting APCs in tissue, thus favoring a breakdown of T-cell anergy and subsequent autoimmunity. Tissue injury caused by infections and other triggers can also alter the presentation of tissue antigens by MHC molecules on resting APCs in tissue, thus favoring a breakdown of T-cell anergy and subsequent autoimmunity. Local tissue injury for any reason can also lead to autoimmunity by exposing self-antigens and autoimmune responses.

Clearly, there is no lack of possible mechanisms to explain how infectious agents might participate in the development of autoimmune diseases. However, there is no evidence that clearly implicates any microbe in the causation of human autoimmune diseases. Recent suggestions (based largely on epidemiologic data) that infections may participate in the development of autoimmune diseases, notably type 1 diabetes and multiple sclerosis. The possible mechanisms are still unclear.

An autoimmune response may itself promote further autoimmune attack by a process that has been called "epitope spreading." A protein has relatively few antigenic determinants (epitopes) that are effectively processed and presented. When a protein is broken down into peptides, many more epitopes are available. If a response to a particular epitope is initiated, and if the response is not controlled, the immune system may begin to react to other epitopes from the same protein or to epitopes from other proteins. This process is called "epitope spreading." Tissue injury caused by an autoimmune response or any other cause may lead to the release of self-antigens that are subsequently presented to T cells in an immunogenic form. The activation of such autoreactive T cells may lead to further tissue injury because the immune response "spreads" to epitopes that were not recognized initially. The process is called "epitope spreading."

response may be maintained by recruitment of autoreactive T cells that recognize these normally

## SUMMARY

### Immunological Tolerance and Autoimmunity

Tolerance (unresponsiveness) to self-antigens is a fundamental property of the immune system. A breakdown of tolerance is the basis of autoimmune diseases. *Central tolerance*: lymphocytes that recognize self-antigens in the central (generative) lymphoid organs undergo apoptosis; in the B-cell lineage, some of the self-reactive lymphocytes switch to become non-self-reactive. *Peripheral tolerance*: mature lymphocytes that reach peripheral tissues become functionally inactive (anergic), or are suppressed by regulatory lymphocytes, or die by apoptosis. The variables that lead to a failure of self-tolerance include (1) inheritance of susceptibility genes, (2) defects in tolerance pathways, and (3) infections and tissue alterations that may expose self-antigens to activate APCs and lymphocytes in the tissues.

Against this general background, the individual systemic autoimmune diseases will be discussed separately; it will be apparent that there is considerable overlap in their clinical, serologic, and molecular features. In this chapter, the autoimmune diseases that affect single organs are discussed in the chapters that deal with the relevant organs.

### Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of protean manifestations. It is an unpredictable, remitting and relapsing disease of acute or insidious onset that may involve virtually any organ. It affects principally the skin, kidneys, serosal membranes, joints, and heart. Immunologically, the disease is characterized by a wide array of autoantibodies, classically including *antinuclear antibodies (ANAs)*. The clinical presentation of SLE overlaps with other autoimmune diseases (rheumatoid arthritis, polymyositis, and others) and its diagnosis is based on the diagnostic criteria for SLE (Table 5-8). The diagnosis is established if a patient demonstrates four or more of the following observations.

SLE is a fairly common disease; its prevalence may be as high as 1 case per 2500 persons in certain populations. In most diseases, there is a strong (approximately 9 : 1) female preponderance, affecting 1 in 700 women in the general population and 1 in 245 women in that group. Its usual onset is in the third decade of life, but it may manifest at any age, including early childhood.

#### *Etiology and Pathogenesis*

*The fundamental defect in SLE is a failure to maintain self-tolerance.* Consequently, a large number of autoantibodies are produced that damage tissues either directly or in the form of immune complex deposits. Understanding the natural history of the disease and for understanding the pathogenesis of the lesions.

#### Spectrum of Autoantibodies in SLE

Antibodies have been identified against a host of nuclear and cytoplasmic components of the cell. Another group of antibodies is directed against surface antigens of blood cells, while yet another group is directed against phospholipids (antiphospholipid antibodies; Chapter 4).

#### Antinuclear Antibodies

ANAs are directed against several nuclear antigens and can be grouped into four categories: (1) antibodies to DNA, (2) antibodies to histones, (3) antibodies to nonhistone proteins bound to RNA, and (4) antibodies to nucleolar antigens. The association of ANAs with SLE as well as with other autoimmune diseases to be discussed later. Severely affected patients may have a high titer of ANAs. Clinically, the most commonly used method is indirect immunofluorescence, which detects antibodies against nuclear antigens, including DNA, RNA, and proteins (*generic ANAs*). The pattern of nuclear fluorescence in the patient's serum, and four basic patterns are recognized:



Homogeneous or diffuse staining usually reflects antibodies to chromatin, histones, and double-stranded DNA. Peripheral staining patterns are most commonly indicative of antibodies to double-stranded DNA. Speckle pattern refers to the presence of uniform or variable-sized speckles. It reflects the presence of antibodies to nuclear proteins such as histones and ribonucleoproteins (RNPs). Nucleolar pattern refers to the presence of antibodies to nucleolar RNA. This pattern is reported most frequently in patients with Sjögren's syndrome.

The immunofluorescence test for ANAs is positive in virtually every patient with SLE, so that the test is not specific, because patients with other autoimmune diseases (and 5% to 15% of normal persons) also have positive ANA tests. Moreover, the fluorescence patterns are not absolutely specific for the type of antibody, and because many combinations frequently exist. It should be noted that the presence of antibodies to dsDNA, or to the Sm antigen, is virtually diagnostic of SLE.

#### Other Autoantibodies

**Table 5-8. 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus**

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis-convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or Pericarditis-documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5gm/dL or >3+ if quantitation not performed or Cellular casts-may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, electrolyte imbalance) or Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia: with reticulocytosis, or Leukopenia: <4.0 × 10 <sup>9</sup> cells per liter (4000 cells per mm <sup>3</sup> ) total on two or more occasions or Lymphopenia: <1.5 × 10 <sup>9</sup> cells per liter (1500 cells per mm <sup>3</sup> ) on two or more occasions or Thrombocytopenia: <100 × 10 <sup>9</sup> cells per liter (100 × 10 <sup>3</sup> cells per mm <sup>3</sup> ) in the absence of drugs known to be associated with drug-induced lupus syndrome
10. Immunologic disorder	Anti-DNA antibody to native DNA in abnormal titer or Anti-Sm: presence of antibody to Sm nuclear antigen or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM antiphospholipid antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis at least 6 months and confirmed by negative <i>Treponema pallidum</i> immobilization or fluorescent antibody test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay of drugs known to be associated with drug-induced lupus syndrome

\*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have SLE if at least 4 of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Data from Tan EM, et al.: The revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271, 1982; and the College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40:1725, 1997.

Antibodies against blood cells, including red cells, platelets, and lymphocytes, are found in many patients with SLE. These antibodies can cause hemolytic anemia, thrombocytopenia, and leukopenia.

present in 40% to 50% of lupus patients and react with a wide variety of proteins in complex with histone antigen, used in serologic tests for syphilis, and therefore lupus patients may have a false-positive test. Antiphospholipids are required for blood clotting, patients with antiphospholipid antibodies may also have false-positive tests, such as the partial thromboplastin time. Therefore, these antibodies are referred to as "lupus anticoagulants." Patients who have them actually have a prothrombotic state (the *antiphospholipid antibody syndrome*), which can lead to venous and arterial thromboses, thrombocytopenia, and recurrent spontaneous miscarriages.

## Immunologic Factors

**Table 5-9. Antinuclear Antibodies in Various Autoimmune Diseases\***

Nature of Antigen	Antibody System	Disease, % Positive			
		SLE	Drug-Induced LE	Systemic Sclerosis-Diffuse	Limited Sclerosis (CREST)
Many nuclear antigens (DNA, RNA, proteins)	Generic ANAs (indirect IF)	>95	>95	70-90	70-90
Native DNA	Anti-dsDNA	40-60	<5	<5	<5
Histones	Antihistone	50-70	>95	<5	<5
Core proteins of small nuclear ribonucleoprotein particles (Smith antigen)	Anti-Sm	20-30	<5	<5	<5
Ribonucleoprotein (U1RNP)	Nuclear RNP	30-40	<5	15	10
RNP	SS-A (Ro)	30-50	<5	<5	<5
RNP	SS-B (La)	10-15	<5	<5	<5
DNA topoisomerase I	Scl-70	<5	<5	28-70	10-18
Centromeric proteins	Anticentromere	<5	<5	22-36	90
Histidyl-tRNA synthetase	Jo-1	<5	<5	<5	<5

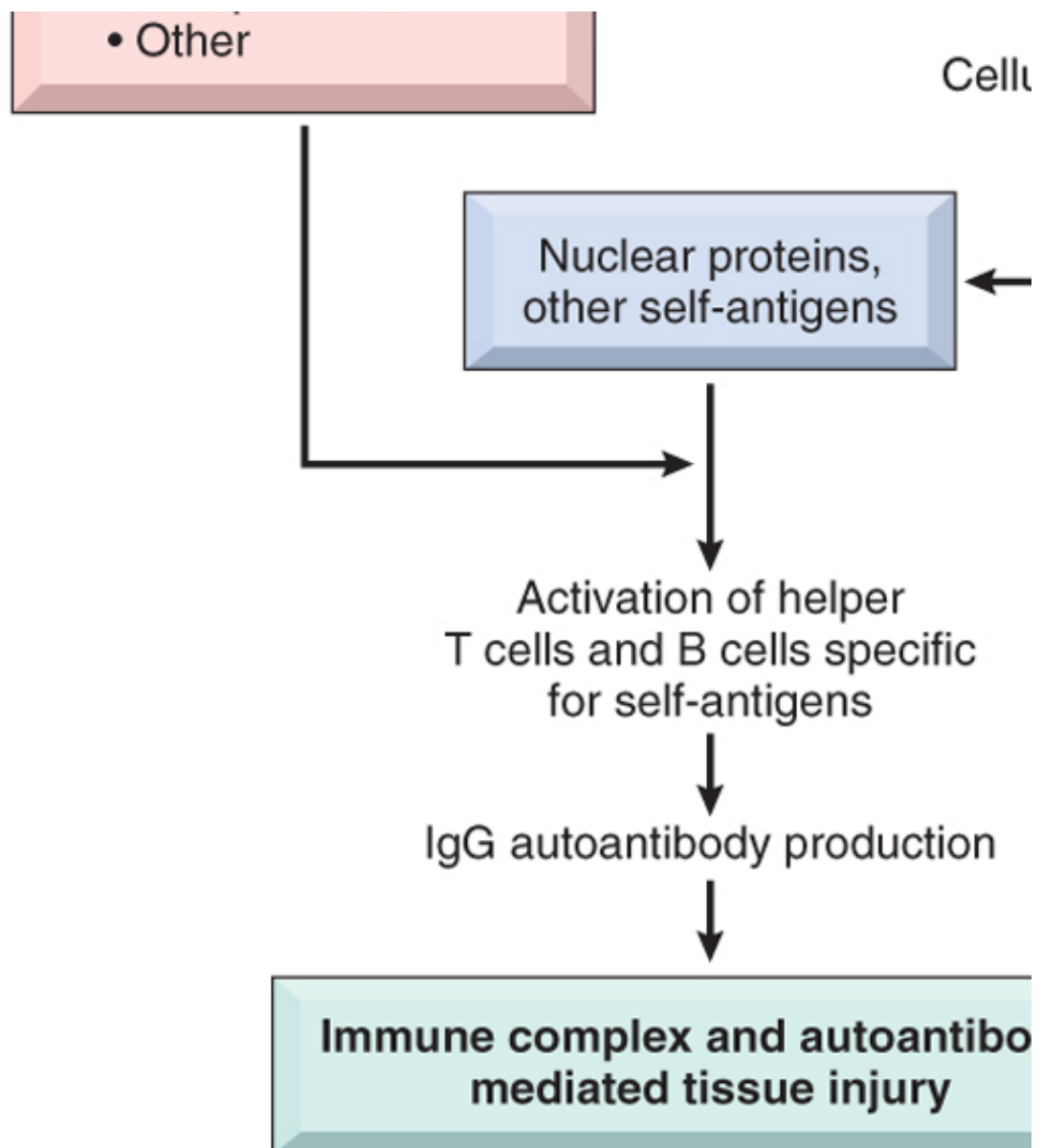
\*Boxed entries indicate high correlation.

ANA, antinuclear antibodies; dsDNA, double-stranded DNA; IF, immunofluorescence; LE, lupus erythematosus; RNP, ribonucleoprotein.

**Inherited susceptibility genes**

- Class II MHC
- Complement

**Environmental factors (e.g.,)**



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 Figure 5-20 Model for the pathogenesis of systemic lupus erythematosus (SLE). The importance of apoptotic cells ;  
 susceptibility genes promote activation of self-reactive lymphocytes is unknown. (Modified from Kotzin BL: Syster  
 1996, with permission from Elsevier.)

All the immunologic findings in SLE patients clearly suggest that some fundamental derangement pathogenesis. *One model for the pathogenesis of the disease proposes a combination of increase nuclear antigens released from apoptotic cells, and a failure of T- and B-cell tolerance to these se* a variety of reported T- and B-cell immunologic abnormalities in SLE patients, it has not been pos For years, intrinsic B-cell hyperactivity was considered a central feature of SLE pathogenesis. How antibodies indicate that they are high-affinity, isotype-switched antibodies whose production requi thought that tolerance has failed in both CD4+ helper T cells and B cells specific for nuclear (and mechanisms for failure of tolerance remain unknown. Recent studies indicate that the peripheral k of overproduction of the cytokine IFN- $\alpha$  and of increased responses to this cytokine. IFN- $\alpha$  is an a innate immune response to many viruses. The relevance of the "interferon signature" to the devel unexplained. Persistent activation of B cells by self nucleoproteins engaging Toll-like receptors ha autoantibody production.

## Genetic Variables

Many lines of evidence support a genetic predisposition to SLE.

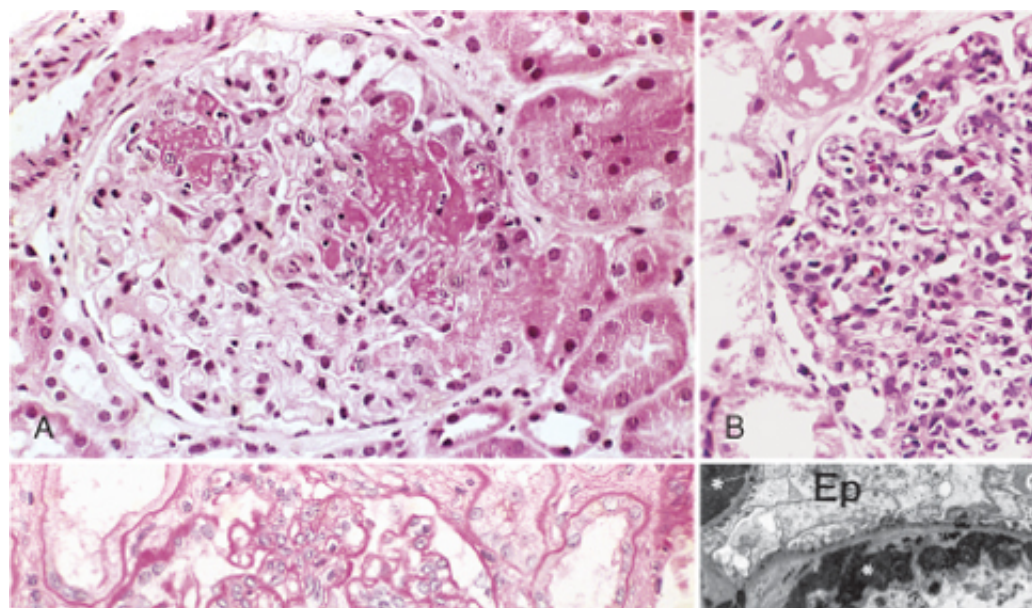
There is a high rate of concordance in monozygotic twins (25%) versus dizygotic twins (1%) increased risk of developing SLE, and up to 20% of clinically unaffected first-degree relatives. In American white populations there is a positive association between SLE and class II HLA  $\epsilon$  locus. Some lupus patients (about 6%) have inherited deficiencies of complement components that impair removal of immune complexes from the circulation and favors tissue deposition, given that the C3 component of complement is involved in phagocytosis of apoptotic cells, and its deficiency impairs removal of, and hence, of nuclear antigens. In mouse models of SLE, different genes are believed to influence the production of specific anti-DNA antibodies, and end-organ damage to the kidneys. The homologous genes

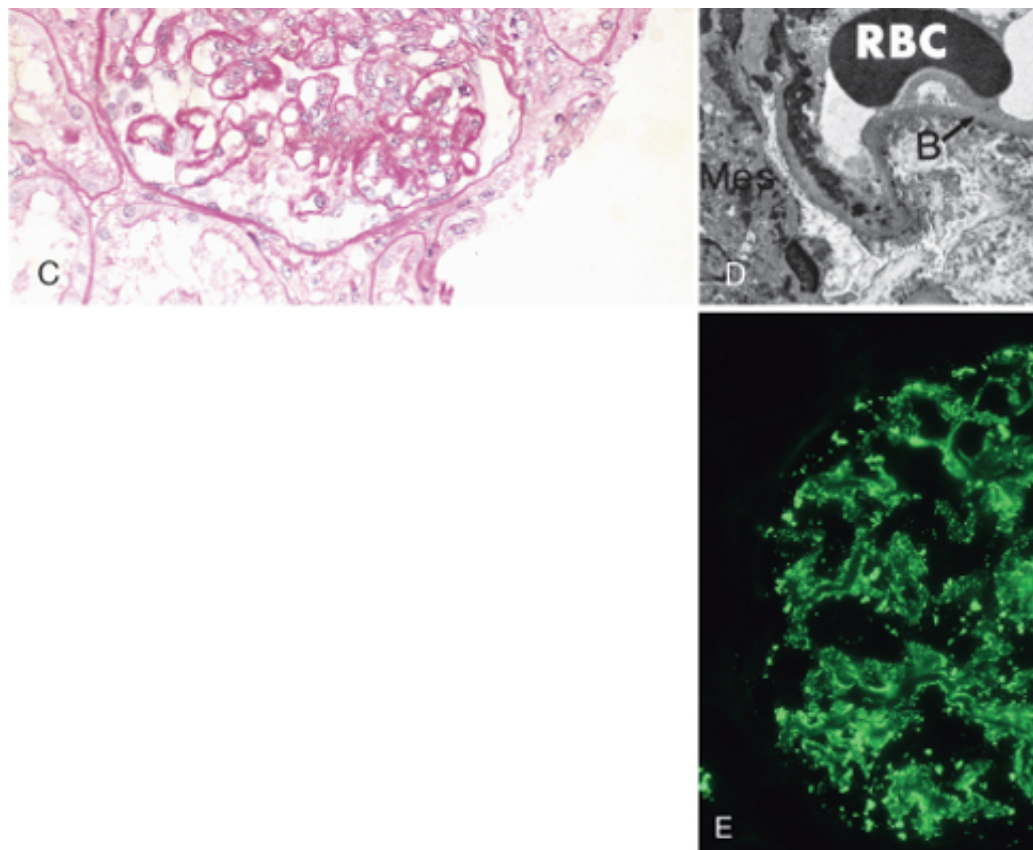
## Nongenetic Variables

*Ultraviolet (UV) radiation* (sun exposure) exacerbates the lesions of SLE. A postulated mechanism is that UV radiation causes apoptosis of host cells, leading to an increased burden of nuclear fragments (see Fig. 5-20). An environmental variable in initiating SLE is the occurrence of a lupus-like syndrome in patients receiving procainamide and hydralazine. Most patients treated with procainamide for more than 6 months develop SLE appearing in 15% to 20% of them. *Sex hormones* also seem to exert an important influence on the disease, with the overwhelming female preponderance of the disease. The mechanism of this hormonal effect is not known.

### *Mechanisms of Tissue Injury*

Regardless of the exact sequence by which autoantibodies are formed, they are clearly the mediators of tissue lesions. Immune complexes (type III hypersensitivity). DNA/anti-DNA complexes (type III hypersensitivity). Serum levels of complement coupled with granular complement deposits in the glomeruli further sustain the disease. In addition, autoantibodies against red cells, white cells, and platelets promote destruction (type II hypersensitivity). There is no evidence that the ANAs involved in immune complex formation bind to cell nuclei are exposed, the ANAs can bind to them. In tissues, nuclei of damaged cells react with antibodies to become homogeneous, to produce so-called *LE bodies* or *hematoxylin bodies*. An in vitro correlation shows that a macrophage that has engulfed the denatured nucleus of another injured cell. When blood is withdrawn, leukocytes are sufficiently damaged to expose their nuclei to ANAs, with secondary complement activation. Complement-opsonized nuclei are then readily phagocytosed. Although the LE cell test is positive in SLE, it is now largely of historical interest.





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Figure 5-21 Lupus nephritis. **A**, Focal proliferative glomerulonephritis, with two focal necrotizing lesions at the 11 Diffuse proliferative glomerulonephritis. Note the marked increase in cellularity throughout the glomerulus (H&E sta several "wire loop" lesions representing extensive subendothelial deposits of immune complexes (periodic acid-glomerular capillary loop from a patient with SLE nephritis. Subendothelial dense deposits correspond to "wire loop antibody in a granular pattern, detected by immunofluorescence. B, basement membrane; End, endothelium; mesangium; RBC, red blood cell in capillary lumen; US, urinary space; \*, electron-dense deposits in subendothelia Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. **D**, Courtesy of Dr. Edwin Eigh Texas, Southwestern Medical School, Dallas. **E**, Courtesy of Dr. Jean Olson, Department of Pathology, Univer

### Morphology

SLE is a systemic disease with protean manifestations (see [Table 5-8](#)). The morph therefore extremely variable and depend on the nature of the autoantibodies, the ti complexes deposit, and the course and duration of disease. The most characterist result from the deposition of immune complexes in a variety of tissues.

An **acute necrotizing vasculitis** affecting small arteries and arterioles may be pre arteritis is characterized by necrosis and by fibrinoid deposits within vessel walls c complement fragments, and fibrinogen; a transmural and perivascular leukocytic in present. In chronic stages, vessels show fibrous thickening with luminal narrowing.

**Kidney involvement is one of the most important clinical features of SLE**, with most common cause of death. The focus here is on glomerular pathology, although lesions are also seen in SLE.

The pathogenesis of all forms of **glomerulonephritis** in SLE involves deposition o complexes within the glomeruli. These evoke an inflammatory response that may c endothelial, mesangial, and/or epithelial cells and, in severe cases, necrosis of the kidney appears normal by light microscopy in 25% to 30% of cases, almost all cas renal abnormality if examined by immunofluorescence and electron microscopy. At Health Organization morphologic classification, there are five patterns of glomerula which is specific to the disease): class I, normal by light, electron, and immunofluo



which is specific to the disease). **class I**, normal by light, electron, and immunofluorescence (less than 5% of SLE patients); **class II**, mesangial lupus glomerulonephritis; **class III**, focal proliferative glomerulonephritis; **class IV**, diffuse proliferative glomerulonephritis; and **class V**, membranous glomerulonephritis.

**Mesangial lupus glomerulonephritis (class II)** is seen in 10% to 25% of cases as a clinical symptoms. Immune complexes deposit in the mesangium, with a slight increase in matrix and cellularity.

**Focal proliferative glomerulonephritis (class III)** is seen in 20% to 35% of cases; it suggests, lesions are visualized in only portions of fewer than half the glomeruli. Types within an otherwise normal glomerulus show swelling and proliferation of endothelial cells, infiltration by neutrophils, and/or fibrinoid deposits with capillary thrombi (Fig. 5-21A). Focal proliferative glomerulonephritis is usually associated with only mild microscopic hematuria and a more diffuse form of renal involvement is associated with more severe disease.

**Diffuse proliferative glomerulonephritis (class IV)** is the most serious form of renal involvement and also the most common, occurring in 35% to 60% of patients. Most of the glomeruli show mesangial proliferation affecting the entire glomerulus, leading to diffuse hypercellularity (Fig. 5-21B), producing in some cases epithelial crescents that fill Bowman's space. Immune complexes create an overall thickening of the capillary wall, resembling rigid "wire loops" on light microscopy (Fig. 5-21C). Electron microscopy reveals electron-dense subendothelial deposits (between endothelium and basement membrane; Fig. 5-21D). Immune complexes stain with fluorescent antibodies directed against immunoglobulins or complement components, showing a granular fluorescent staining pattern (Fig. 5-21E). In due course, glomerular injury gives rise to glomerulosclerosis. Most of these patients have hematuria with moderate to severe proteinuria, hypertension, and renal insufficiency.

**Membranous glomerulonephritis (class V)** occurs in 10% to 15% of cases and is a chronic glomerular disease characterized by widespread thickening of the capillary wall. Membranous glomerulonephritis associated with SLE is very similar to that encountered in idiopathic membranous nephropathy (Chapter 14). Thickening of capillary walls is caused by increased deposition of subendothelial membrane-like material, as well as accumulation of immune complexes. Patients with membranous glomerulonephritis almost always have severe proteinuria with overt nephrotic syndrome (Chapter 14).

The **skin** is involved in the majority of patients; a characteristic erythematous or malar rash on the cheeks, nose, and chin (the malar eminences and bridge of the nose ("butterfly pattern")) is observed in about 50% of patients. Exposure to sunlight (UV light) exacerbates the erythema (so-called **photosensitivity**), and a similar rash may occur elsewhere on the extremities and trunk, frequently in sun-exposed areas. Histologically, there is hyperkeratosis, degeneration of the basal layer of the epidermis, edema at the dermoepidermal junction, and perivascular infiltrates around blood vessels and skin appendages (Fig. 5-22A). Immunofluorescence shows granular deposition of Ig and complement at the dermoepidermal junction (Fig. 5-22B); similar findings may also be present in apparently uninvolved skin.

**Joint involvement** is frequent but is usually not associated with striking anatomic deformity. When present, it consists of swelling and a nonspecific mononuclear cell infiltrate in the synovial membranes. Erosion of the membranes and destruction of articular cartilage, such as in rheumatoid arthritis, is exceedingly rare.

**Central nervous system (CNS) involvement** is also very common, with focal neurologic and neuropsychiatric symptoms. CNS disease is often ascribed to vascular lesions caused by cerebral microinfarcts. Small vessel angiopathy with noninflammatory intimal proliferation is a frequent pathological lesion; frank vasculitis is uncommon. The angiopathy may be caused by antiphospholipid antibodies. Premature atherosclerosis occurs, and may lead to stroke or myocardial infarction. It has also been postulated that anti-neuronal antibodies cause neuronal damage. The pathogenesis remains unproved.

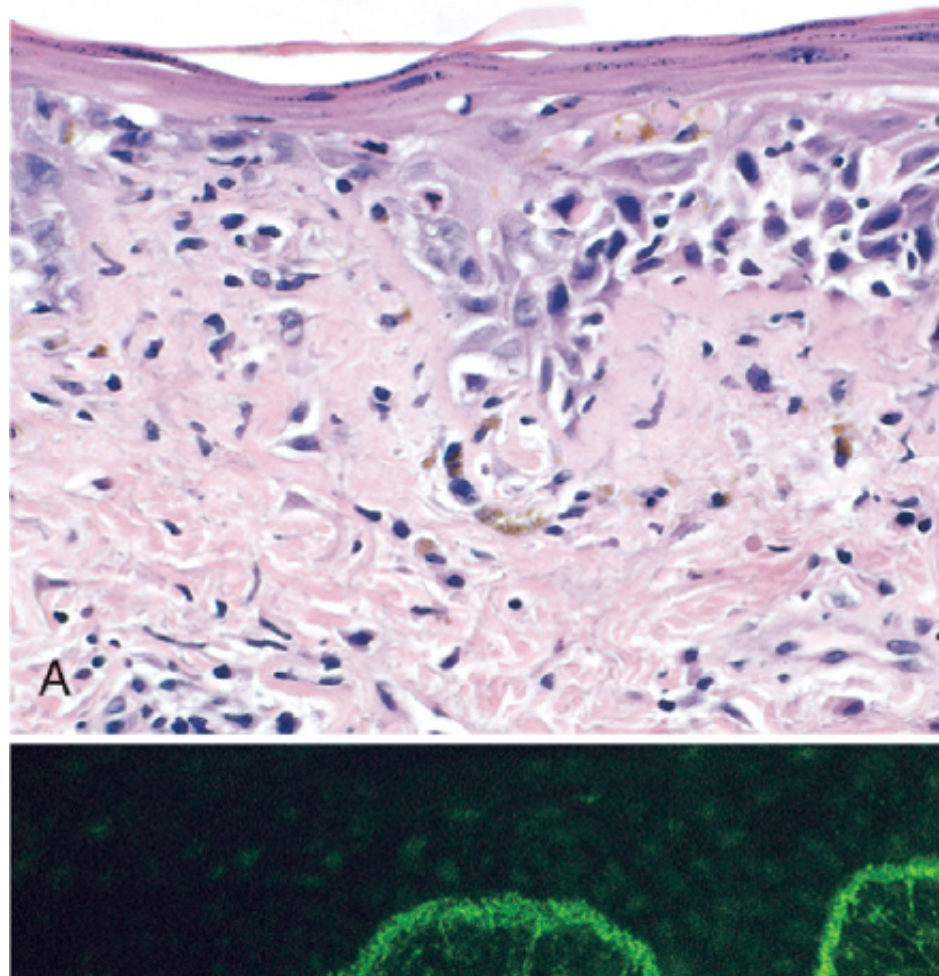
hypertension remains unproved.

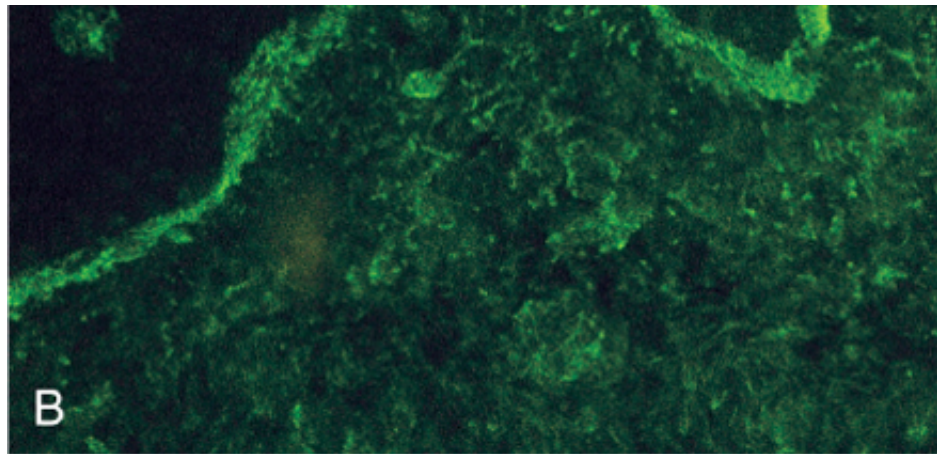
The **spleen** may be moderately enlarged. Capsular fibrous thickening is common, with numerous plasma cells in the red pulp. Central penicilliary arteries characteristically show perivascular fibrosis, producing **onion-skin lesions**.

Pericardium and pleura, in particular, are **serosal membranes** that show a variety of changes in SLE ranging (in the acute phase) from serous effusions to fibrinous exudates and opacification in the chronic stage.

**Involvement of the heart** is manifested primarily in the form of pericarditis. Myocarditis, a nonspecific mononuclear cell infiltrate, and valvular lesions, called **Libman-Sacks** endocarditis, but are less common in the current era of aggressive corticosteroid therapy. The valvular **verrucous endocarditis** takes the form of irregular, 1- to 3-mm warty deposits, distributed along the free margins of the leaflets (i.e., on the surface exposed to the forward flow of the blood or on the surface of the leaflets). An increasing number of patients also show clinical and anatomical evidence of coronary artery disease. The basis of accelerated atherosclerosis is not fully understood; it is multifactorial; certainly, immune complexes can deposit in the coronary vasculature and cause damage by that pathway. Moreover, glucocorticoid treatment causes alterations in lipid metabolism. Renal disease (common in SLE) causes hypertension; both of these are risk factors for atherosclerosis (Chapter 10).

Many **other organs and tissues** may be involved. The changes consist essentially of inflammation of small vessels, foci of mononuclear infiltrations, and fibrinoid deposits. In addition, there is pleural fibrosis, along with pleural inflammation; the liver shows nonspecific inflammation and





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Figure 5-22 SLE involving the skin. **A**, An H&E-stained section shows liquefactive degeneration of the basal layer at the dermoepidermal junction. **B**, An immunofluorescence micrograph stained for IgG reveals deposits of Ig along the dermoepidermal junction. **B**, Courtesy of Dr. Richard Sontheimer, I. M. D., Boston University School of Medicine, Boston, Massachusetts. **B**, Courtesy of Dr. Richard Sontheimer, I. M. D., Southwestern Medical School, Dallas, Texas.)

### *Clinical Manifestations*

The diagnosis of SLE may be obvious in a young woman with a classic butterfly rash over the face and photosensitivity. However, in many patients the presentation of SLE is subtle and puzzling, taking the form of fever, unknown origin, abnormal urinary findings, or neuropsychiatric manifestations, including psychosis. Renal involvement, including hematuria, red cell casts, proteinuria, and, in some cases, the development of glomerulonephritis (see Table 5-8). Renal failure may occur, especially in patients with diffuse proliferative or membranous glomerulonephritis. Renal derangements mentioned (see Table 5-8) may in some cases be the presenting manifestation as ANAs can be found in virtually 100% of patients, but they can also be found in patients with other autoimmune diseases. Anti-dsDNA antibodies and antibodies to the so-called Smith (Sm) antigen are considered highly specific for SLE. ANA levels are low, typically as a result of deposition of immune complexes.

The course of SLE is extremely variable. Even without therapy, some patients follow a relatively benign course with mild manifestations and/or mild hematuria. Rare cases rapidly progress to death within months. Most patients have remissions and relapses spanning years to decades. Acute flare-ups are usually controlled by steroids. Overall, with current therapies, 90% five-year and 80% ten-year survivals can be expected. Renal and CNS involvement are the major causes of death.

## **SUMMARY**

### **Systemic Lupus Erythematosus**

SLE is a systemic autoimmune disease caused by autoantibodies produced against self-antigens and the formation of immune complexes. The major autoantibodies for the formation of circulating immune complexes, are directed against nuclear antigens. Autoantibodies react with erythrocytes, platelets, and various complexes of proteins. Disease manifestations include nephritis, skin lesions and arthritis (caused by immune complexes), and hematologic and neurologic abnormalities. The breakdown in self-tolerance in SLE is unknown; it may include excess or deficiency of regulatory T cells, multiple inherited susceptibility genes, and environmental triggers which results in cellular apoptosis and release of nuclear proteins).

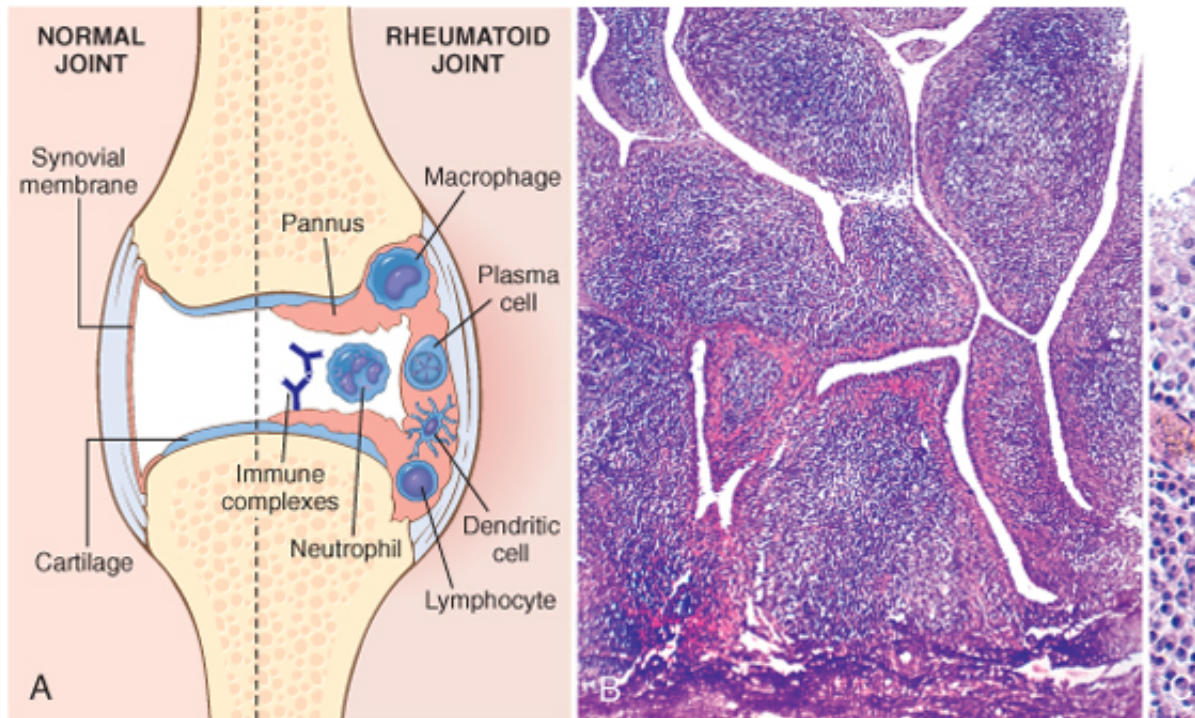
### **Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease affecting many tissues but primarily the joints.



a *nonsuppurative proliferative synovitis that frequently progresses to destroy articular cartilage and arthritis*. When extra-articular involvement develops—for example, of the skin, heart, blood vessels, SLE or scleroderma.

RA is a very common condition, with a prevalence of approximately 1%; it is three to five times more common in women than in men. The peak incidence is in the second to fourth decades of life, but no age is immune. Morphology will be discussed in the context of pathogenesis.



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Figure 5-23 Rheumatoid arthritis. **A**, A joint lesion. **B**, Low magnification reveals marked synovial hypertrophy with dense lymphoid aggregates in the synovium. (**A**, Modified with permission from Feldmann M: Developmental Immunology 2:364, 2002.)

## Morphology

A broad spectrum of morphologic alterations is seen in RA; the most severe occur in the small joints of the hands, wrists, elbows, and shoulders. Typically, the proximal interphalangeal and metacarpophalangeal joints are affected, but distal interphalangeal joints are spared. Axial involvement, when it occurs, is limited to the upper cervical spine; similarly, hip joint involvement is extremely uncommon. Histologic studies show **chronic synovitis**, characterized by (1) synovial cell hyperplasia and proliferation; (2) perivascular inflammatory cell infiltrates (frequently forming lymphoid follicles) in the synovium; (3) increased vascularity due to angiogenesis; and (4) aggregates of organizing fibrin on the synovial surface and in the joint space; (5) osteoclast activity in the underlying bone, leading to synovial penetration and bone erosion. The appearance is that of a **pannus**, formed by proliferating synovial-lining cells admixed with granulation tissue, and fibrous connective tissue; the overgrowth of this tissue is so extensive that the usually thin, smooth synovial membrane is transformed into a thick, edematous, friable mass (Fig. 5-23). With full-blown inflammatory joint involvement, periarticular soft tissue is also affected. The disease is classically manifested first by fusiform swelling of the proximal interphalangeal joint. In advanced disease, the articular cartilage subjacent to the pannus is eroded and, in time, virtually all articular bone may also be attacked and eroded. Eventually the pannus fills the joint space, and subsequent **fibrosis and calcification** may cause permanent **ankylosis**. The radiographic

subsequent **fibrosis and calcification** may cause permanent **ankylosis**. The late joint effusions and juxta-articular osteopenia with erosions and narrowing of the joint articular cartilage. Destruction of tendons, ligaments, and joint capsules produces deformities, including radial deviation of the wrist, ulnar deviation of the fingers, and abnormalities of the fingers (swan-neck deformity, boutonnière deformity).

**Rheumatoid subcutaneous nodules** develop in about one-fourth of patients, occur on the surface of the forearm or other areas subjected to mechanical pressure; rarely they occur on the spleen, heart, aorta, and other viscera. Rheumatoid nodules are firm, nontender, and can be as large as 2 cm in diameter. Microscopically, they are characterized by a central focus of necrosis surrounded by a palisade of macrophages, which in turn is rimmed by granulation tissue.

Patients with severe erosive disease, rheumatoid nodules, and high titers of **rheumatoid factor** (IgM that binds IgG; see later) are at risk of developing vasculitic syndromes; acute and chronic forms involve small or large arteries. Serosal involvement may manifest as fibrinous pleuritis. Lung parenchyma may be damaged by progressive interstitial fibrosis. Ocular changes include keratoconjunctivitis (similar to those seen in Sjögren syndrome; see later) may be present.

### *Pathogenesis*

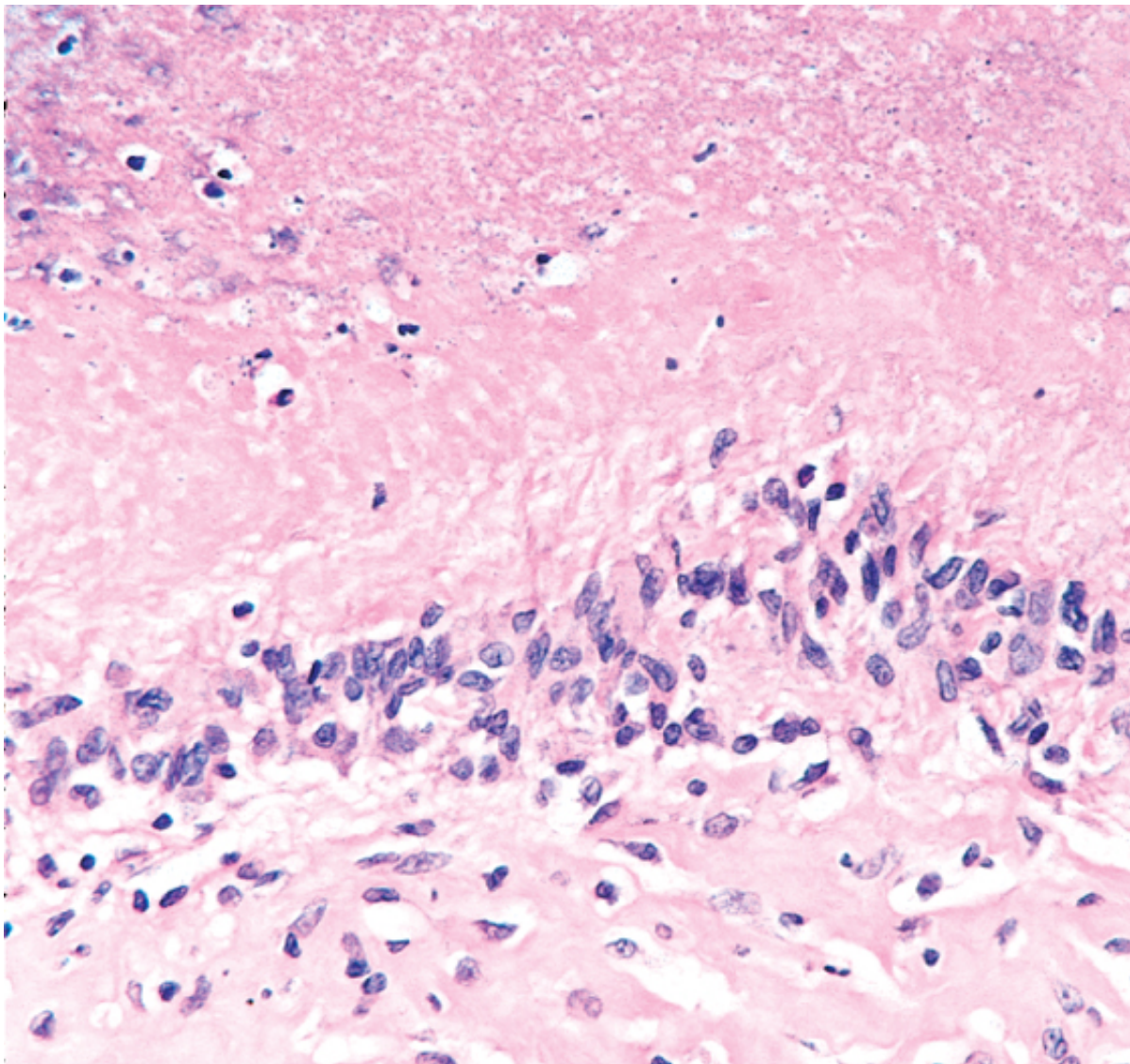




Figure 5-24 Rheumatoid nodule. Subcutaneous nodule with an area of necrosis (*top*) surrounded by a palisade of r cells.

The joint inflammation in RA is immunologically mediated, and there is a clear genetic predisposition to agents and the precise interplay between genetic and environmental variables are not yet understood. In a genetically predisposed individual, by activation of *CD4+* *helper T cells* responding to microbial, or to some self-antigen (Fig. 5-25). The activated T cells produce *cytokines* that (1) act in joint space, releasing degradative enzymes and other factors that perpetuate inflammation, and (2) production of antibodies, some of which are directed against self-antigens in the joint. The rheumatoid factor (RF) and macrophage-derived cytokines. The activity of these cytokines accounts for many features of RA: TNF, promote leukocyte recruitment, others activate macrophages, and yet others, such as IL-1, activate fibroblasts. The cytokines also stimulate secretion by synovial cells and chondrocytes of proteolytic enzymes. Activated T cells in RA lesions have also been shown to express impressive amounts of a cytokine that promotes osteoclast differentiation and activation and may play a key role in the bone resorption seen in RA. Despite the plethora of cytokines produced in the joint in RA, TNF appears to play a pivotal role. The effectiveness of TNF antagonists in the disease, even in patients who are resistant to other therapies.

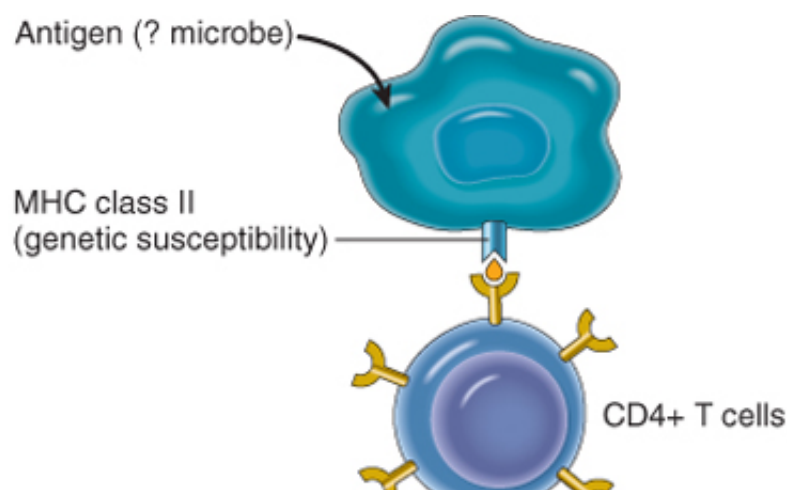
The role of *antibodies* in the disease is suspected from a variety of experimental and clinical observations. Serum IgM (and, less frequently, IgG) autoantibodies that bind to the Fc portions of their own (self) IgG, called *rheumatoid factor (RF)*. They may form immune complexes with self-IgG that deposit in joints and cause tissue damage. However, the role of RF in the pathogenesis of the joint or extra-articular lesions is unclear. 20% of patients do not have RF, suggesting that these autoantibodies are not essential for tissue damage.

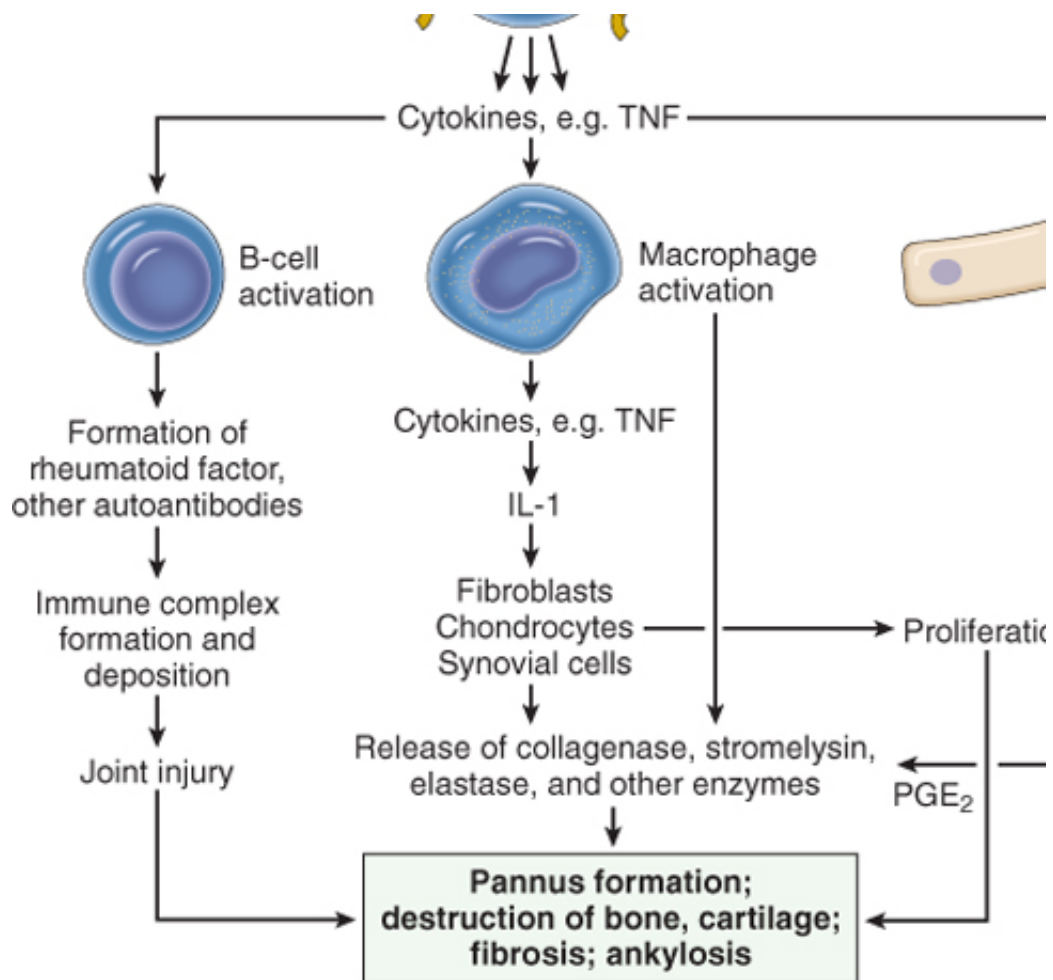
*Genetic variables* in the pathogenesis of RA are suggested by the increased frequency of this disease in monozygotic twins; there are also associations of *HLA-DR4* and polymorphisms in other genes.

Finally, there are the elusive *infectious agents* whose antigens may activate T or B cells. Many candidates have been conclusively proved. Suspects include EBV, *Borrelia* species, *Mycoplasma* species, parvovirus B19, and others.

### Clinical Course

Although RA is basically a symmetric polyarticular arthritis, there may also be constitutional symptoms such as low-grade fever. Many of the systemic manifestations result from the same mediators that cause joint inflammation. The arthritis first appears insidiously, with aching and stiffness of the joints, particularly in the morning. The joints become enlarged, motion is limited, and in time complete ankylosis may appear. Vascular involvement includes *Raynaud phenomenon* and chronic leg ulcers. Such multisystem involvement must be distinguished from dermatomyositis, and Lyme disease, as well as other forms of arthritis. Helpful in making the correct diagnosis are (1) radiographic findings; (2) sterile, turbid synovial fluid with decreased viscosity, poor mucin clot formation; and (3) RF (80% of patients).





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 Figure 5-25 Model for the pathogenesis of rheumatoid arthritis. CD4+ T cells reacting against an unknown antigen lead to autoantibody production and to activate macrophages and other cells in the joint synovium.

The clinical course of RA is highly variable. In a minority of patients the disease may become static, but in the remainder it pursues a chronic, remitting-relapsing course. The natural history of the disease has been leading to disability after 10-15 years. However, the outcome has been dramatically improved by the aggressive treatment of early RA and the introduction of highly effective biologic agents that antagonize reactive amyloidosis (discussed later), which develops in 5% to 10% of these patients, particularly

## SUMMARY

### Rheumatoid Arthritis

RA is a chronic inflammatory disease that affects mainly the joints, especially the small joints of the hands and feet. The disease is caused by an autoimmune response to an unknown antigen(s), which leads to T-cell reactions in the joint with production of cytokines and activation of macrophages and other cells that damage tissues and stimulate proliferation of synovial cells. TNF plays a central role, and antagonists against TNF are of great benefit. IL-1 and PGE<sub>2</sub> also contribute to the disease.

### Juvenile Rheumatoid Arthritis

Juvenile RA (JRA) refers to chronic idiopathic arthritis that occurs in children. It is not a single disease but a group of disorders, most of which differ significantly from the adult form of RA except for the destructive nature of the disease.

as are rheumatoid nodules. Extra-articular inflammatory manifestations such as uveitis may be present in a few larger joints such as knees, elbows, and ankles and are thus called *pauciarticular*. Some cases and their clinical features overlap with the spondyloarthropathies described next. One variant, prefebrile onset and systemic manifestations, including leukocytosis (white blood cell counts of 15,000/mm<sup>3</sup>), lymphadenopathy, and rash.

### Seronegative Spondyloarthropathies

For years, several entities in this group of disorders were considered variants of RA; however, careful studies have distinguished these disorders from RA. The spondyloarthropathies are characterized

Pathologic changes that begin in the ligamentous attachments to bone rather than in the synovial joints, with or without arthritis in other peripheral joints  
Absence of RFs (hence the name "seronegative spondyloarthropathies")  
Association with *HLA-B27*

This group of disorders includes several clinical entities, of which *ankylosing spondylitis* is the prototype. Other entities include psoriatic arthritis, spondylitis associated with inflammatory bowel diseases, and reactive arthropathies (associated with *Shigella*, *Salmonella*, *Helicobacter*, or *Campylobacter*). Sacroiliitis is a common manifestation in a group distinguished by the particular peripheral joints involved, as well as by associated extraskelatal manifestations (conjunctivitis, and uveitis are characteristic of Reiter syndrome). Although a triggering infection may underlie most of the seronegative spondyloarthropathies, their pathogenesis remains obscure.

### Sjögren Syndrome

Sjögren syndrome is a clinicopathologic entity characterized by dry eyes (*keratoconjunctivitis sicca*) from immune-mediated destruction of the lacrimal and salivary glands. It occurs as an isolated disease (*sicca syndrome*), or more often in association with another autoimmune disease (secondary form). The most common, but some patients have SLE, polymyositis, systemic sclerosis, vasculitis, or thy-

#### *Etiology and Pathogenesis*

Several lines of evidence suggest that Sjögren syndrome is an autoimmune disease in which the exocrine glands are the primary target. Nevertheless, there is also systemic B-cell hyperactivity, as evidenced by the presence of autoantibodies (even in the absence of associated RA). Most patients with primary Sjögren syndrome have autoantibodies to SS-A (Ro) and SS-B (La); note that these antibodies are also present in some SLE patients and are therefore not specific for Sjögren (see Table 5-9). Although patients with high-titer anti-SS-A antibodies are more likely to have systemic disease, there is no evidence that the autoantibodies cause primary tissue injury. Analogous to SLE as well as to loss of tolerance in the CD4<sup>+</sup> T-cell population, although the nature of the target autoantigen is unclear, suggested, but no causative virus has been identified conclusively. *Genetic variables* play a role in the disease. As with SLE, inheritance of certain class II MHC alleles predisposes to the development of specific

#### **Morphology**

Lacrimal and salivary glands are the primary targets, but other secretory glands, including the parathyroid glands, nasopharynx, upper airway, and vagina, may also be involved. Involved tissues show a mixed infiltrate of (primarily activated CD4<sup>+</sup> T cells) and plasma-cell infiltrate, occasionally forming lymphoid follicles with germinal centers. There is associated destruction of the native architecture (Fig. 5-10).

Lacrimal gland destruction results in a lack of tears, leading to drying of the cornea and subsequent inflammation, erosion, and ulceration (**keratoconjunctivitis**). Similar changes occur in the oral mucosa as a result of loss of salivary gland output, giving rise to mucosal atrophy, fissuring and ulceration (**xerostomia**). Dryness and crusting of the nose may lead to perforation of the nasal septum. When the respiratory passages are involved, secondary chronic bronchitis, and pneumonitis may appear. Approximately 25% of the patients (especially those with high-titer autoantibodies) develop extraglandular disease affecting the CNS, skin, kidneys, and in the form of mild interstitial nephritis associated with tubular transport defects; unlike systemic lupus erythematosus, glomerulonephritis is rare.

### Clinical Course

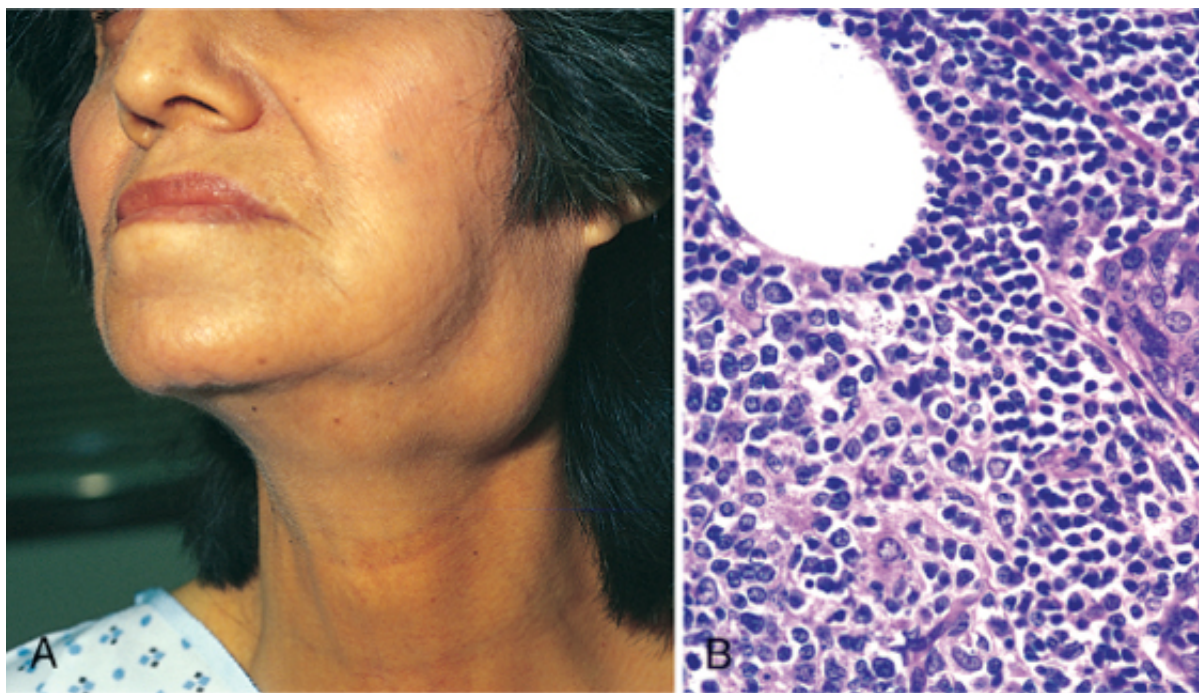
Approximately 90% of Sjögren syndrome cases occur in women between the ages of 35 and 45 years, characterized by a lack of tears, and the resultant complications just described. Salivary glands are often enlarged as (Fig. 5-26). Extraglandular manifestations include synovitis, pulmonary fibrosis, and peripheral neuropathy. Many patients have an accompanying autoimmune disorder such as RA. Notably, there is a 40-fold increased risk of developing lymphoma, arising in the setting of the initial robust polyclonal B-cell proliferation. These so-called lymphoproliferative disorders are discussed in Chapter 12.

### SUMMARY

#### Sjögren Syndrome

Sjögren syndrome is an inflammatory disease that affects primarily the salivary glands, causing dryness of the mouth and eyes. The disease is believed to be caused by an autoimmune cell reaction against an unknown self antigen(s) expressed in these glands, or against the antigens of a virus that infects the tissues.

### Systemic Sclerosis (Scleroderma)



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Figure 5-26 Sjögren syndrome. **A**, Enlargement of the salivary gland. **B**, The histologic view shows intense lymphocytic infiltration and epithelial hyperplasia. (**A**, Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical Center; **B**, Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical Center)

Although commonly called *scleroderma*, this disorder is better labeled systemic sclerosis (SS), because it involves fibrosis throughout the body and not just the skin. Cutaneous involvement is the usual presenting feature in approximately 95% of cases, but it is the visceral involvement—of the gastrointestinal tract, lungs, and kidneys—that produces the major morbidity and mortality.

SS can be classified into two groups based on its clinical course:



*Diffuse scleroderma*, characterized by initial widespread skin involvement, with rapid progression. *Limited scleroderma*, with relatively mild skin involvement, often confined to the face and extremities. The disease in these patients generally has a fairly benign course because of its frequent features of calcinosis, Raynaud phenomenon, esophageal dysmotility, and telangiectasia.

### *Etiology and Pathogenesis*

*Fibroblast activation with excessive fibrosis is the hallmark of systemic sclerosis.* The cause is unknown. It is proposed that CD4<sup>+</sup> cells responding to an as yet unidentified antigen accumulate in the skin and release fibrogenic cytokines such as IL-1, PDGF, TGF- $\beta$ . The possibility that activated T cells play a role in the pathogenesis of SS is supported by the observation that similar changes (including the cutaneous sclerosis) are seen in chronic GVHD, a disorder resulting from sustained allogeneic bone marrow transplants. B-cell activation also occurs, as indicated by the presence of ANA. Although humoral immunity does not play any significant role in the pathogenesis of SS, two of the ANA are disease specific and are therefore useful in diagnosis (see Table 5-9). One of these, directed against DNA topoisomerase I, is present in as many as 70% of patients with diffuse scleroderma (and in less than 1% of other autoimmune diseases) and is a marker for patients likely to develop more aggressive disease with pulmonary fibrosis. The other ANA is an *anticentromere antibody*, found in as many as 90% of patients with limited scleroderma and indicates a relatively benign course.

Microvascular disease is also consistently present early in the course of SS, although the mechanism is mysterious. It is possible that endothelial cells are activated and subsequently injured by the local release of endothelial damage followed by platelet aggregation lead to release of platelet factors (e.g., PDGF) and narrowing of the microvasculature, with eventual ischemic injury.

### **Morphology**

Virtually any organ may be affected in SS, but the most prominent changes are found in the musculoskeletal system, gastrointestinal tract, lungs, kidneys, and heart.

**Skin.** The vast majority of patients have diffuse, sclerotic atrophy of the skin, usually involving the hands and distal regions of the upper extremities and extending proximally to involve the neck, and face. In the early stages, affected skin areas are somewhat edematous and firm to touch. Histologically, there is edema and perivascular infiltrates containing mononuclear cells. Small arteries (as large as 500  $\mu$ m in diameter) may show thickening of the basement membrane, intimal hyperplasia, and partial occlusion. With progression, the edematous phase is replaced by a phase of sclerosis, in which the dermis becomes tightly bound to the subcutaneous structures. There is deposition of compact collagen in the dermis along with thinning of the epidermis, atrophy of the dermal papillae, and hyaline thickening of the walls of dermal arterioles and capillaries (Fig. 5-27A, B). In advanced stages, diffuse subcutaneous calcifications may develop, especially in patients with the CR form. In advanced stages the fingers take on a tapered, clawlike appearance with limitation of motion (Fig. 5-27C), and the face becomes a drawn mask. Loss of blood supply may lead to atrophic changes in the terminal phalanges, including autoamputation.

**Gastrointestinal Tract.** The gastrointestinal tract is affected in approximately 90% of patients. Atrophy and collagenous fibrous replacement of the muscularis may develop at any site, but is most severe in the esophagus, with the lower two-thirds often developing an inflexible, dilated, and tortuous "bird's beak" appearance. The associated dysfunction of the lower esophageal sphincter gives rise to gastroesophageal reflux and its complications, including Barrett metaplasia (Chapter 15) and strictures. The stomach may be ulcerated, and there is excessive collagenization of the lamina propria and atrophy of the gastric pits and microvilli in the small bowel is the anatomic basis for the malabsorption syndrome encountered.

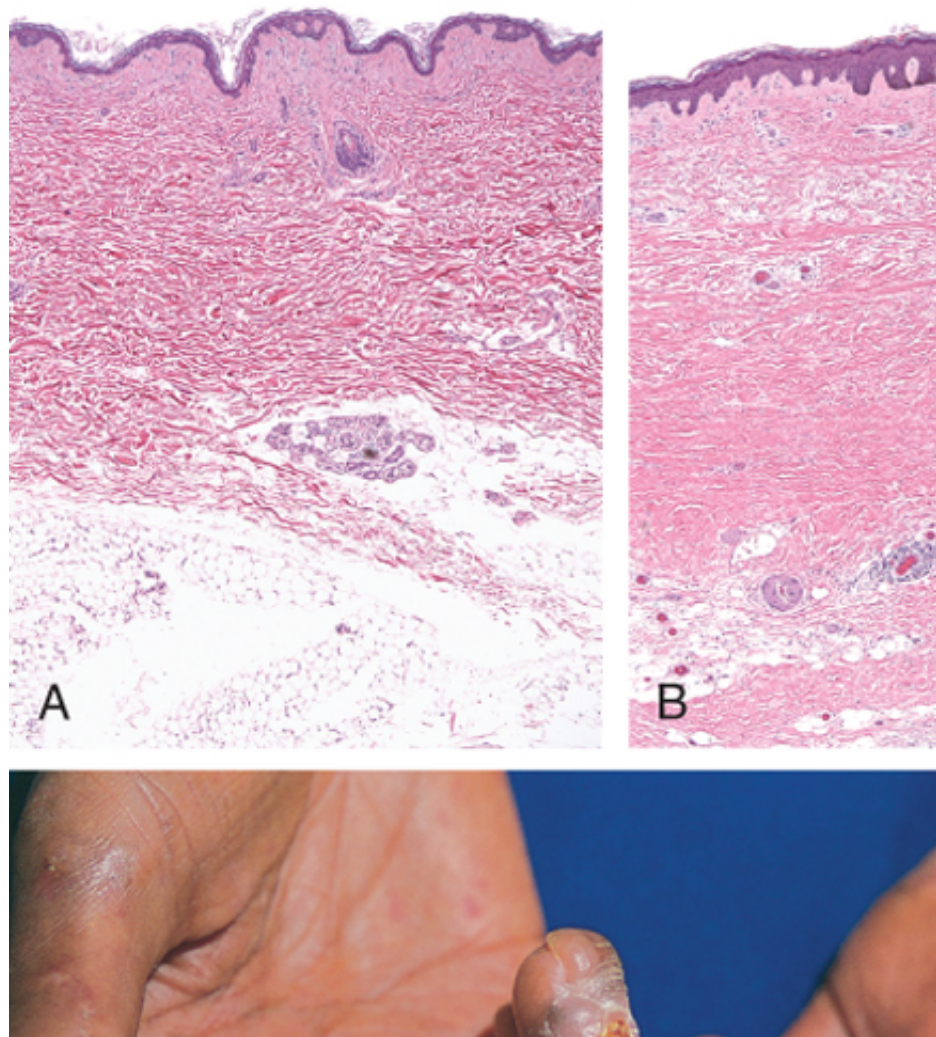
**Musculoskeletal System.** Synovial hyperplasia and inflammation is common in the early stages of SS. Although these changes are reminiscent of RA, joint destruction is not

later ensues. Although these changes are reminiscent of RA, joint destruction is not seen in a small subset of patients (approximately 10%), inflammatory myositis is not seen, and osteoarthritis develops.

**Lungs.** The lungs are affected in more than 50% of patients; this may manifest as and/or interstitial fibrosis. Pulmonary vasospasm from pulmonary vascular endothelial dysfunction is considered important in the pathogenesis of pulmonary hypertension. Pulmonary fibrosis is indistinguishable from that seen in idiopathic pulmonary fibrosis ([Chapter 13](#)).

**Kidneys.** Renal abnormalities occur in two-thirds of patients with SS, most typically thickening of the vessel walls of interlobular arteries (150-500  $\mu$ m in diameter). The proliferation with deposition of various glycoproteins and acid mucopolysaccharide changes seen in malignant hypertension, the alterations in SS are restricted to vessel diameter and are not always associated with hypertension. Hypertension does occur in 20% of those patients; it takes an ominously malignant course (malignant hypertension). In patients, vascular alterations are more pronounced and are often associated with fibrin thrombi in the arterioles together with thrombosis and infarction. Such patients often die of renal failure; about half the deaths in patients with SS. There are no specific glomerular changes.

**Heart.** Patchy myocardial fibrosis, along with thickening of intramyocardial arterioles, occurs in the patients; this is putatively caused by microvascular injury and resultant ischemia (Raynaud). Because of the changes in the lung, right ventricular hypertrophy and failure are frequent.





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 Figure 5-27 Systemic sclerosis. **A**, Normal skin. **B**, Extensive deposition of dense collagen in the dermis. **C**, The immobilized the fingers, creating a clawlike flexion deformity. Loss of blood supply has led to cutaneous ulcers.  
 Department of Dermatology, University of Texas Southwestern Medical School, I

### Clinical Course

SS affects women three times more often than men, with a peak incidence in the 50- to 60-year age group. In presentation between SS and RA, SLE, and dermatomyositis (see later); the distinctive feature is skin involvement. Almost all patients develop *Raynaud phenomenon*, a vascular disorder characterized by episodic color changes in the fingers. Typically the hands turn white on exposure to cold, reflecting vasospasm, followed by a blue color. Finally, the color changes to red as reactive vasodilation occurs. Progressive collagenization of the skin leads to increasing stiffness and eventually complete immobilization of the joints. Difficulty in swallowing results from resultant hypomotility. Eventually, destruction of the esophageal wall leads to atony and dilation. Malabsorption due to submucosal and muscular atrophy and fibrosis involve the small intestine. Dyspnea and chronic cough are signs of advanced lung involvement, secondary pulmonary hypertension may develop, leading to right-sided heart failure. Impairment secondary to both the advance of SS and the concomitant malignant hypertension is frequent.

The course of diffuse SS is difficult to predict. In most patients the disease pursues a steady, slow course over many years, although in the absence of renal involvement, life span may be normal. The overall 10-year survival rate is about 50%. The chances of survival are significantly better for patients with localized scleroderma than for those with diffuse disease. *Limited scleroderma*, or CREST syndrome, frequently has Raynaud phenomenon as its most prominent feature. Its limited skin involvement confined to the fingers and face, and these two features may be present without visceral lesions.

### SUMMARY Systemic Sclerosis

Systemic sclerosis (commonly called *scleroderma*) is characterized by progressive fibrosis of the skin, gastrointestinal tract, and other tissues. Fibrosis may be the result of excessive deposition of collagen by cytokines produced by T cells, but what triggers T-cell responses is unknown. Microvascular disease is commonly present in the lesions of systemic sclerosis, leading to chronic ischemia, but the pathogenesis of vascular injury is not known.

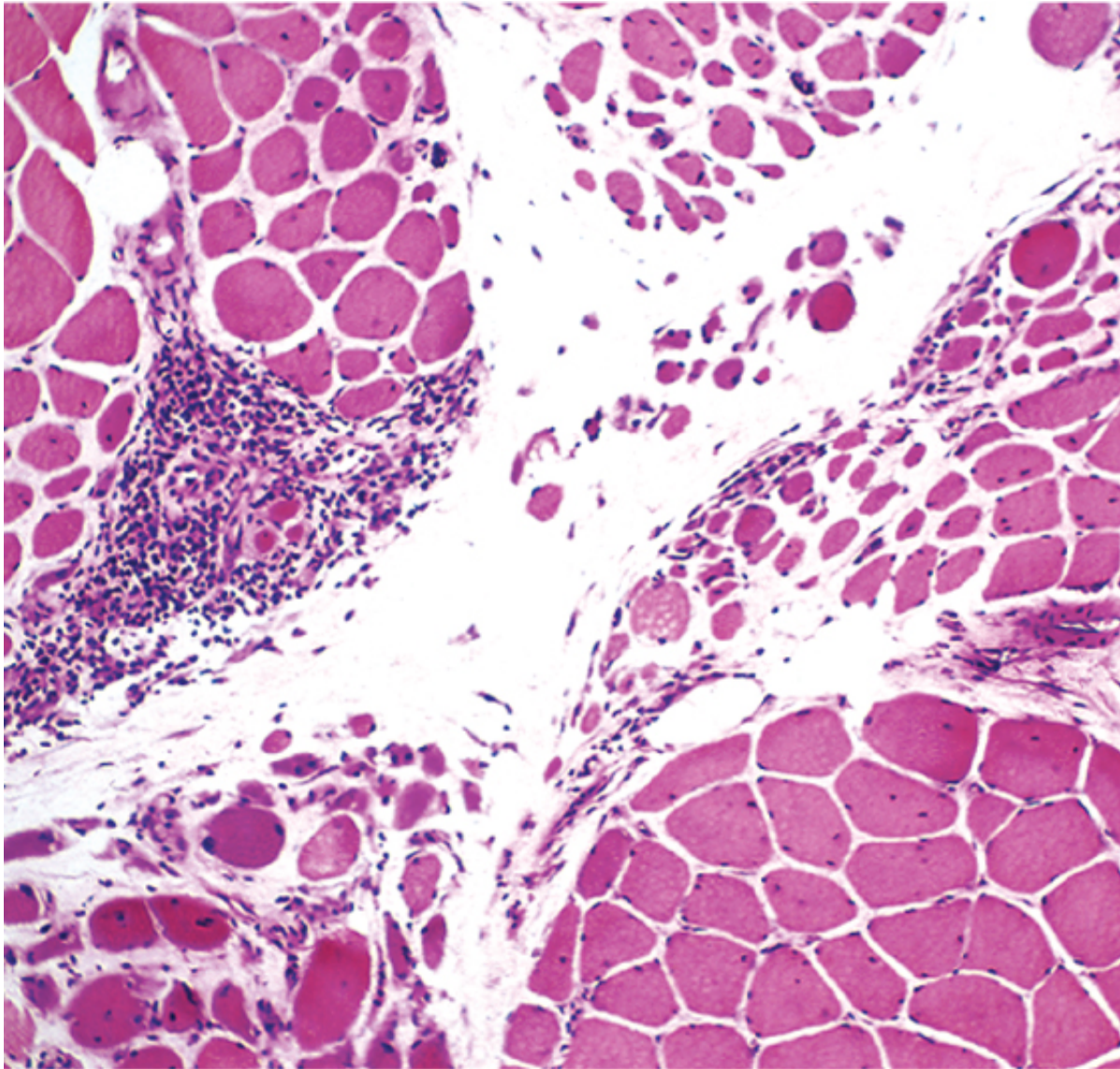
### Inflammatory Myopathies

Inflammatory myopathies make up a heterogeneous group of rare disorders characterized by immune-mediated muscle inflammation. Based on the clinical, morphologic, and immunologic features, three disorders—*polymyositis*, *dermatomyositis*, and *inclusion body myositis*—have been described. These may occur alone or in conjunction with other autoimmune diseases. Patients with dermatomyositis have a slightly increased risk of developing visceral cancers (of the lung, ovary, and stomach).

Clinically, these diseases are characterized by usually symmetric muscle weakness initially affecting the proximal muscles.



Clinically, these diseases are characterized by usually symmetric muscle weakness initially affecting the proximal limbs. Thus, tasks such as getting up from a chair or climbing steps become increasingly difficult. A skin rash (classically described as a *lilac* or *heliotrope* discoloration) affects the upper eyelids and causes periorbital edema. In the muscle, there is perivascular and perifascicular infiltration by lymphocytes, and both degenerating and regenerating muscle fibers are seen (Fig. 5-28). The location of the inflammatory infiltrates are fairly distinctive for each subtype.



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Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis J. Storch, Texas Southwestern Medical School, Dallas, Texas.)

The immunologic evidence supports antibody-mediated tissue injury in dermatomyositis, whereas polymyositis seems to be mediated by CTLs. ANAs are present in most patients. Of these, only Jo-1 antibodies, anti-synthetase, are specific for this group of disorders (see Table 5-9).

The diagnosis of these myopathies is based on clinical features, laboratory evidence of muscle injury (elevated creatine kinase), electromyography, and biopsy.

### Mixed Connective Tissue Disease

The term *mixed connective tissue disease* refers to a spectrum of pathologic processes in patients with clinical features suggestive of SLE, polymyositis, and SS; they also have high titers of antibodies to an RNP.



features suggestive of SLE, polymyositis, and SS, they also have high titers of antibodies to all the features of mixed connective tissue disease are the paucity of renal disease and an extremely good prognosis which suggest a favorable long-term prognosis.

Mixed connective tissue disease may present as arthritis, swelling of the hands, Raynaud phenomenon, leukopenia and anemia, fever, lymphadenopathy, and/or hypergammaglobulinemia. Because of the unclear whether mixed connective tissue disease constitutes a distinct disease or represents heterosclerosis, and polymyositis; most authorities do not consider it a specific entity.

### **Polyarteritis Nodosa and Other Vasculitides**

Polyarteritis nodosa belongs to a group of diseases characterized by necrotizing inflammation of the vessel wall in an immune pathogenesis. The general term *noninfectious necrotizing vasculitis* differentiates these diseases from direct vessel infection (e.g., an abscess) and serves to emphasize that any type of vessel may be involved. A detailed classification and description of vasculitides is presented in [Chapter 10](#).



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## IMMUNE DEFICIENCY DISEASES

Immune deficiency diseases may be caused by inherited defects affecting immune system development, or secondary effects of other diseases (e.g., infection, malnutrition, aging, immunosuppression, autoimmune diseases). Patients with immune deficiency present with increased susceptibility to infections as well as to certain cancers. The severity of infections in a given patient depends largely on the component of the immune system that is affected. Defects in the complement, or phagocytic cells typically suffer from recurrent infections with pyogenic bacteria, and defects in humoral immunity are prone to infections caused by viruses, fungi, and intracellular bacteria. Here we discuss the most important primary immune deficiencies, followed by a detailed description of the acquired immune deficiency syndrome (AIDS), a devastating example of secondary immune deficiency.

### Primary Immune Deficiencies

Primary immune deficiency states are (fortunately) rare but have nevertheless contributed greatly to our understanding of the structure and function of the immune system. Most primary immune deficiency diseases are genetically determined defects of either humoral or cellular immunity (i.e., humoral or cellular) or innate host defense mechanisms, including complement proteins and natural killer (NK) cells. Defects in adaptive immunity are often subclassified on the basis of the primary component affected (humoral or cellular); however, because of the interactions between T and B lymphocytes, these distinctions are frequently blurred. Deficiencies frequently lead to impaired antibody synthesis, and hence isolated deficiencies of T cells may be associated with deficiencies of B cells. Most primary immune deficiencies come to attention early in life (but not always), usually because the affected infants are susceptible to recurrent infections. One of the most important advances in molecular biology has been the identification of the genetic basis of many primary immune deficiencies, which has led to the development of future gene replacement therapy.

### ***X-Linked Agammaglobulinemia (XLA, Bruton Disease)***

X-Linked agammaglobulinemia (XLA), or Bruton disease, is one of the more common forms of primary immune deficiency. It is characterized by the failure of pre-B cells to differentiate into B cells; as a consequence, there is an absence of gamma globulin in the blood. During normal B-cell maturation, Ig heavy-chain genes undergo a series of rearrangements. At each stage, signals are received from the expressed components of the antigen receptor complex. If these signals are not received, the process stops at the next stage; these signals act as quality controls, to ensure that the correct receptor proteins are being produced. In XLA, the process stops after the initial heavy-chain gene rearrangement because of mutations in a tyrosine kinase that encodes the pre-B-cell receptor and is involved in pre-B-cell signal transduction. This kinase is called *Bruton tyrosine kinase* (*BTK*). If it is nonfunctional, the pre-B-cell receptor cannot signal the cells to proceed along the maturation pathway, and the complete Ig molecule containing heavy and light chains cannot be assembled. Although free heavy chains can be found in the cytoplasm, because *BTK* maps to the X chromosome, the disease is X-linked.

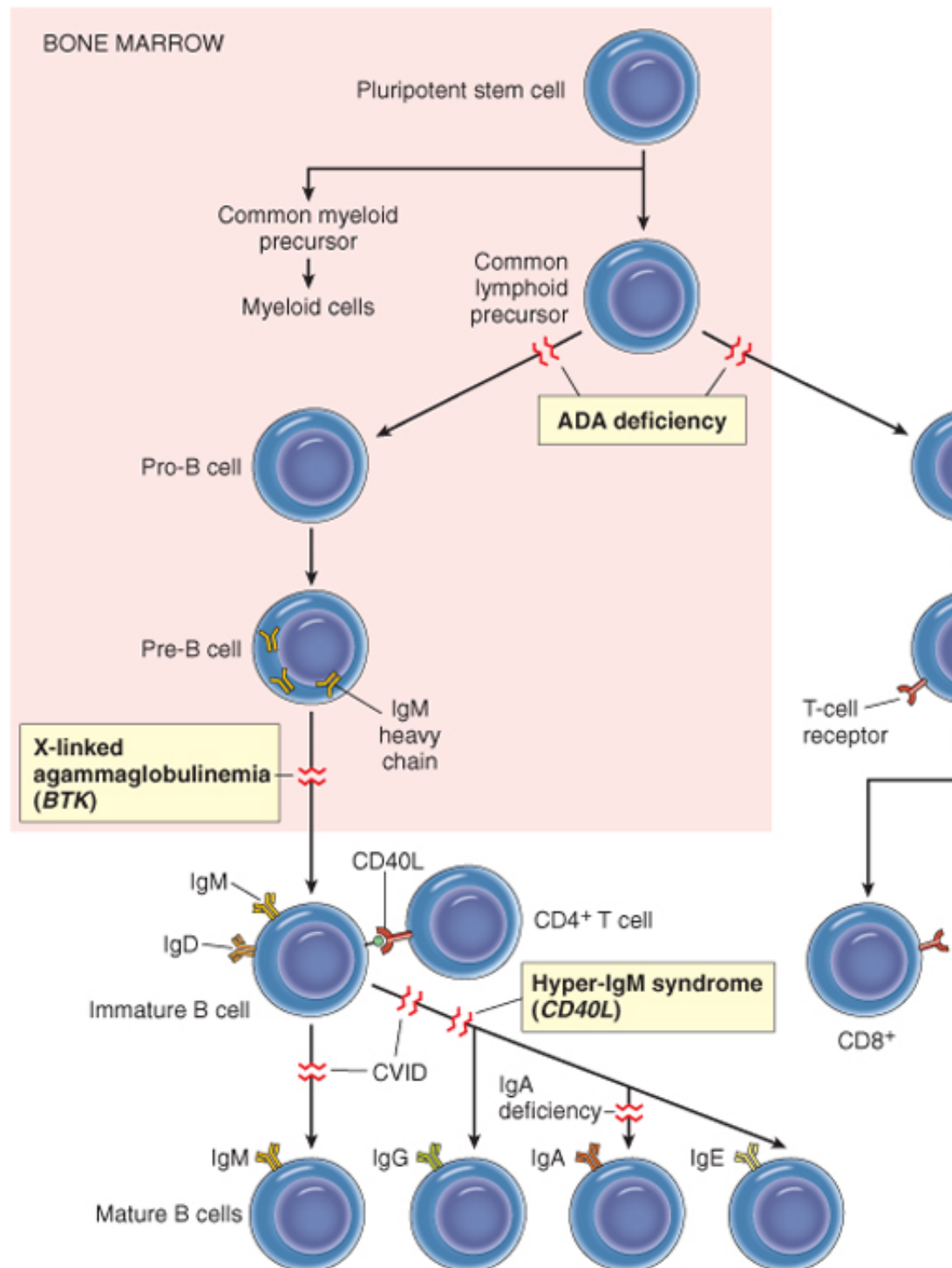
Classically, this disease is characterized by

- Absent or markedly decreased numbers of B cells in the circulation, with depressed serum immunoglobulin levels.
- The numbers of pre-B cells in the bone marrow may be normal or reduced.
- Underdeveloped or absent peripheral lymphoid tissues, including lymph nodes, Peyer patches, the appendix, and tonsils.
- Normal T-cell-mediated responses.

XLA does not become apparent until approximately 6 months of age, when maternal immunoglobulin levels decline. Patients with XLA suffer from recurrent bacterial infections such as acute and chronic pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia. The causal organisms are typically those bacterial pathogens that are dependent on opsonization and phagocytosis (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Staphylococcus aureus*). Because these patients lack antibodies, they are also susceptible to certain viral infections, such as enteroviruses. Similarly, *Giardia lamblia*, an intestinal protozoan usually neutralized by secreted IgA, causes persistent infections. Fortunately, replacement therapy with intravenous Ig from pooled human plasma can adequately combat bacterial infections. Patients with XLA clear most viral, fungal, and protozoan infections because cell-mediated immunity is intact. For unclear reasons, autoimmune diseases (such as RA and dermatomyositis) are not observed in these patients.

patients with this disease.

### **Common Variable Immunodeficiency**



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 Figure 5-29 Primary immune deficiency diseases. Lymphocyte development and sites of block in primary immunodeficiency diseases are indicated in parentheses for some of the disorders. ADA, adenosine<sub>2</sub> deaminase; CD40L, CD40 ligand (also immunodeficiency); SCID, severe combined immunodeficiency.

This is a heterogeneous group of disorders characterized by hypogammaglobulinemia, impaired  $\alpha$  (and  $\beta$ ) vaccination), and increased susceptibility to infections. The clinical manifestations are superficially variable immunodeficiency the sexes are affected equally and the onset of symptoms is much late. The diagnosis is usually one of exclusion (after other causes of immune deficiency are ruled out); (hence the name). Although most patients have normal numbers of mature B cells, plasma cells are stimulated B-cell differentiation. The defective antibody production has been variably attributed to help, or excessive T-cell suppressor activity. Paradoxically, these patients are prone to develop a (hemolytic anemia, pernicious anemia), as well as lymphoid tumors. Some patients with this disease have certain growth factors, or in molecules involved in T cell-B cell interactions. However, the genetic basis is not known.

### ***Isolated IgA Deficiency***

The most common of all the primary immune deficiency diseases, IgA deficiency affects about 1 in 500. It is the major Ig in mucosal secretions and is thus involved in airway and gastrointestinal defense. Although most are asymptomatic, weakened mucosal defenses predispose patients to recurrent sinopulmonary infections. There is a significant (but unexplained) association with autoimmune diseases. The pathogenesis of IgA deficiency involves defective terminal differentiation of IgA-secreting B cells to plasma cells; IgM and IgG subclasses of antibodies are present at supranormal levels. The molecular basis of this defect is not understood.

### ***Hyper-IgM Syndrome***

In a normal immune response to protein antigen, IgM antibodies are produced first, followed by the other isotypes (IgG, IgA, and IgE). As we discussed earlier in this chapter, the orderly appearance of different antibody classes is called *(isotype) switching* and is important for generating classes of antibody that can effectively activate different types of pathogens. The ability of IgM-producing B cells to turn on the transcription of genes that encode cytokines, as well as contact-mediated signals from CD4<sup>+</sup> helper T cells. The contact-dependent interaction between CD40 molecules on B cells and CD40L (also known as CD154), expressed on activated CD4<sup>+</sup> T cells, is critical for isotype switching. In hyper-IgM syndrome, patients produce normal (or even supranormal) levels of IgM antibodies to antigens but lack the other isotypes; the underlying defect is an inability of T cells to induce B-cell isotype switching. The mutation of the gene encoding CD40L. This gene is located on the X chromosome; consequently, hyper-IgM syndrome is X-linked. In the remaining patients, the mutations affect CD40 or other molecules involved in the interaction, notably an enzyme called *activation-induced deaminase*.

Although the disease is diagnosed and named because of the antibody abnormality, there is also a defect in cell-mediated immunity. Because the CD40-CD40L interaction is critical for helper T cell-mediated activation of macrophages and other cells, male patients with the X-linked form of hyper-IgM syndrome present with recurrent pyogenic infections. These patients are also susceptible to a variety of intracellular pathogens, including *Pneumocystis jirovecii* (formerly called *P. carinii*).

### ***Thymic Hypoplasia: DiGeorge Syndrome***

DiGeorge syndrome results from a congenital defect in thymic development with deficient T-cell numbers in the thymus, spleen, and peripheral blood, and infants with this defect are extremely vulnerable to viral infections. They are also susceptible to infection with intracellular bacteria, because of defective T-cell-mediated immunity. Humoral immunity is generally unaffected.

The disorder is a consequence of a developmental malformation affecting the third and fourth pharyngeal pouches, which give rise to the thymus, parathyroid glands, and portions of the face and aortic arch. Thus, in addition to the parathyroid gland hypoplasia resulting in hypocalcemic tetany, as well as additional midline defects, there is a deletion affecting chromosome 22q11, discussed in [Chapter 7](#). Some patients have been successfully treated with thymic transplantation. In patients with partial defects, immunity may improve with age.

### ***Severe Combined Immunodeficiency***

Severe combined immunodeficiency (SCID) represents a constellation of genetically distinct syndromes with defects in both humoral and cell-mediated immune responses. Affected infants are susceptible to



array of pathogens, including bacteria, viruses, fungi, and protozoans; opportunistic infections by *Pseudomonas* also cause serious (and occasionally lethal) disease.

Despite the common clinical features, the underlying defects in individual patients are quite diverse. Some have a single defect affecting both T and B cells, and others may result from a primary T-cell deficit with secondary B-cell immunity. Approximately half of the cases are X-linked; these are caused by mutations in the genes encoding the receptors for the cytokines IL-2, IL-4, IL-7, IL-9, and IL-15. Of these cytokines, IL-7 is the most important as the growth factor responsible for stimulating the survival and expansion of immature B- and T-cell precursors. Another 40% to 50% of SCID cases are inherited in an autosomal recessive fashion, with mutations in *adenosine deaminase (ADA)*, an enzyme involved in purine metabolism. ADA deficiency leads to the accumulation of *adenosine* and deoxyadenosine triphosphate metabolites, which inhibit DNA synthesis and are toxic to lymphocytes. In recessive cases of SCID are attributed to defects in another purine metabolic pathway, primary failure of adenosine deaminase. Mutations in genes encoding the recombinase responsible for the rearrangement of lymphocyte antigen receptor genes are also found in some cases of SCID.

In the two most common forms of SCID (cytokine receptor common  $\gamma$  chain mutation and ADA deficiency), lymph nodes and lymphoid tissues (e.g., in the tonsils, gut, and appendix) are atrophic and lack B and T cells. Affected patients may have marked lymphopenia, with both T- and B-cell deficiencies. In some cases, there are large numbers of immature T cells and/or large numbers of B cells that are nonfunctional because of a lack of function. Patients are currently treated by bone marrow transplantation. X-SCID is the first disease in which gene therapy has been used to replace the mutated gene, but the approach is being re-evaluated because some of the treated patients have developed leukemia, presumably because the introduced gene inserted close to a cellular oncogene.

### ***Immune Deficiency with Thrombocytopenia and Eczema: Wiskott-Aldrich Syndrome***

Wiskott-Aldrich syndrome is an X-linked recessive disease characterized by thrombocytopenia, eczema, and recurrent infection, ending in early death; the only treatment is bone marrow transplantation. This presentation and immunologic deficits are difficult to explain on the basis of the known underlying defects. The presentation is normal, but there is progressive age-related depletion of T lymphocytes in the peripheral blood and defects in cellular immunity. Additionally, patients do not effectively synthesize antibodies to polysaccharide antigens and are susceptible to encapsulated, pyogenic bacteria. (However, B-cell responses to polysaccharide antigens are normal.) Patients are also prone to developing malignant lymphomas. The responsible gene maps to the X chromosome and encodes the *Wiskott-Aldrich syndrome protein* that links several membrane receptors to the cytoskeleton. An inherited defect in this protein could result in abnormal cellular morphology (including platelet shape changes) and impaired activation signals in lymphocytes and other leukocytes, with abnormal cell-cell adhesions and leukocyte migration.

### ***Genetic Deficiencies of Components of Innate Immunity***

Several genetic defects have been shown to affect molecules or cells that are important in the early stages of innate immunity.

#### ***Complement Proteins***

As discussed earlier in this chapter and in [Chapter 2](#), complement components play important roles in host defense responses. Consequently, hereditary deficiency of complement components, especially C3 (critical for both classical and alternative pathways), results in an increased susceptibility to infection with pyogenic bacteria. Inherited deficiencies of complement components (C1-C9) result in recurrent infections by *Neisseria* (gonococci, meningococci). Deficiencies of the complement pathway (C5-C8) result in recurrent infections by *Neisseria*. Lack of the regulatory protein C1 inhibitor allows unfettered C1 activation, with the generation of excessive C3a and C5a mediators; the result is *hereditary angioedema*, characterized by recurrent episodes of localized swelling of mucous membranes.

#### ***Phagocytes***

Several congenital defects in phagocytes are known. These include defects in the phagocyte oxidase system (Chediak-Higashi syndrome), defects in the lysosomal enzymes (mucopolysaccharidoses), and defects in integrins and selectin ligands, causing the *leukocyte adhesion deficiency*, described in [Chapter 2](#).

## **SUMMARY**

## SUMMARY

### Primary (Congenital) Immune Deficiency Diseases

Caused by mutations in genes involved in lymphocyte maturation or function  
immunity Some of the common disorders are

*XLA*: failure of B-cell maturation, absence of antibodies; mutations in *Bruton's tyrosine kinase* encodes B-cell tyrosine kinase, required for maturation signals from T-cell receptors  
*Common variable immunodeficiency*: defects in antibody production; in most cases  
*Selective IgA deficiency*: failure of IgA production; caused by a mutation in the gene encoding T-cell and B-cell maturation; mutation in the common  $\gamma$  chain of a cytokine receptor leads to failure of IL-7 signaling and defective lymphopoiesis  
*Autosomal SCID*: severe combined immunodeficiency; primary defect in lymphocyte development, secondary defect in antibody responses; approximately 1 in 10,000 live births  
*ADA*: mutation in the gene encoding ADA, leading to accumulation of toxic metabolites  
*X-linked hyper-IgM syndrome*: failure of isotype-switched high-affinity antibodies (IgG, IgA, IgE); mutation in *CD40*

Clinical presentation: increased susceptibility to infections in early life

### Secondary Immune Deficiencies

*Immune deficiencies secondary to other diseases or therapies are much more common than the primary immune deficiencies* may be encountered in patients with malnutrition, infection, cancer, renal disease, etc. Common cases of immune deficiency are therapy-induced suppression of the bone marrow and of the thymus.

In the following section, we describe AIDS, an immune deficiency that has become one of the great public health problems of the world.

### Acquired Immunodeficiency Syndrome

AIDS is a retroviral disease caused by the human immunodeficiency virus (HIV). It is characterized by a depletion of lymphocytes, and by profound immunosuppression leading to opportunistic infections, secondary malignancies, and other manifestations. Although AIDS was first described in the United States, it has now been reported worldwide. More than 22 million people have died of AIDS since the epidemic was recognized in 1981. With the disease, and there are an estimated 5 million infections each year. Worldwide, 95% of HIV infections are in Africa alone carrying more than 50% of the HIV burden. Although the largest number of infections in HIV infection in the past decade are in Southeast Asian countries, including Thailand, India, and China, the incidence is slightly better in the industrialized nations; for example, approximately 1 million US citizens are infected. In the United States, more than 500,000 have died of AIDS than died in both world wars combined. Although the incidence has declined from a 1995 peak, AIDS still represents the fifth most common cause of death in adults between 25 and 64 years of age.

Because of the combined work of many scientists and clinicians, there has been an explosion of research on the biology of HIV. So rapid is the pace of research on the biology of HIV that any text covering the topic will probably be out of date before it is published. Nevertheless, the following will attempt to summarize the currently available information on the pathogenesis, and clinical features.

### Epidemiology

Epidemiologic studies in the United States have identified five groups at risk for developing AIDS, except as noted below. Transmission of HIV occurs under conditions that facilitate the exchange of body fluids containing the virus or virus-infected cells. Thus, *the major routes of HIV infection are sexual contact, parenteral transmission from infected mothers to their newborns*. The case distributions listed below are in the United States; the distributions in other countries are unknown or not reported.

Homosexual or bisexual males constitute the largest group of infected individuals, accounting for 56% of infected men (approximately 4% of these also inject drugs). This category is declining, with less than 50% of new cases attributable to male homosexual contact. In other high-risk groups constituted about 34% of infections in 2001-2004. In Africa and Asia, the majority of new cases are in women infected by male partners. Intravenous drug use accounts for about 10% of new cases in the United States.

infections, and the majority of new cases are in women infected by male partners. Intravenous homosexuality compose the next largest group, representing about 17% of all patients. Recipients (but not hemophiliacs) who received transfusions of HIV-infected whole blood or components <1% of patients. Hemophiliacs, especially those who received large amounts of factor VIII concentrate, less than <1% of all cases. The epidemiology of HIV infection and AIDS is quite different in children <13 years of age). About 1% of all AIDS cases occur in this population, and the vast majority of transmission of virus from infected mother to the fetus or newborn.

### *Sexual Transmission*

*Sexual transmission* is by far the major mode of infection worldwide, accounting for more than 75%. Although most sexually transmitted cases in the United States are still due to homosexual or bisexual activity, *sexually transmitted HIV infections globally are due to heterosexual activity*. Even in the United States, heterosexual transmission has outpaced transmission by other means; such spread accounts for the dramatic increase in the number of partners of male intravenous drug abusers.

The virus is present in semen, both extracellularly and within mononuclear inflammatory cells, and in vaginal secretions. Viral transmission can occur either by direct entry of virus or by contact with open wounds or lacerations or abrasions in mucosa. Viral transmission can occur either by direct entry of virus or by contact with open wounds or lacerations or abrasions in mucosa. Clearly, all forms of sexual transmission are aided and abetted by other sexually transmitted diseases that cause genital ulcerations, including syphilis, chancroid, and *Chlamydia* also act as cofactors for HIV transmission, primarily by increasing the seminal fluid carrying HIV). In addition to male-to-male and male-to-female transmission, HIV is present in the vaginal secretions of women and can also be spread from females to males, albeit about eightfold less efficiently.

### *Parenteral Transmission*

*Parenteral transmission* of HIV is well documented in three different groups: intravenous drug abusers, recipients of factor VIII or IX concentrates, and random recipients of blood transfusion. Among intravenous drug abusers, transmission occurs through shared needles, syringes, or other paraphernalia contaminated with HIV-containing blood.

Transmission of HIV by transfusion of blood or blood products such as lyophilized factor VIII concentrates has been reported since 1985. Four public health measures are responsible: screening of donated blood and plasma for HIV, screening for associated p24 antigen (detectable before the development of antibodies), heat treatment of clotting factors, and selection of donors on the basis of history. With all these measures, the risk of transfusion-associated HIV infection has been reduced to roughly 1 in 676,000 donations. This translates into approximately 18 out of 12 million transfusions. In the advent of nucleic acid testing, this already small risk will show further decline.

### *Mother-to-Infant Transmission*

As noted earlier, mother-to-infant *vertical transmission* is the major cause of pediatric AIDS. Three routes of transmission are possible: transplacental spread; intrapartum, during delivery; and via ingestion of HIV-contaminated breast milk. Intrapartum routes account for most cases. Vertical transmission rates worldwide vary from 25% to 30% in the United States; higher rates of infection occur with high maternal viral load and/or the presence of genital ulcers and increasing placental accumulation of inflammatory cells.

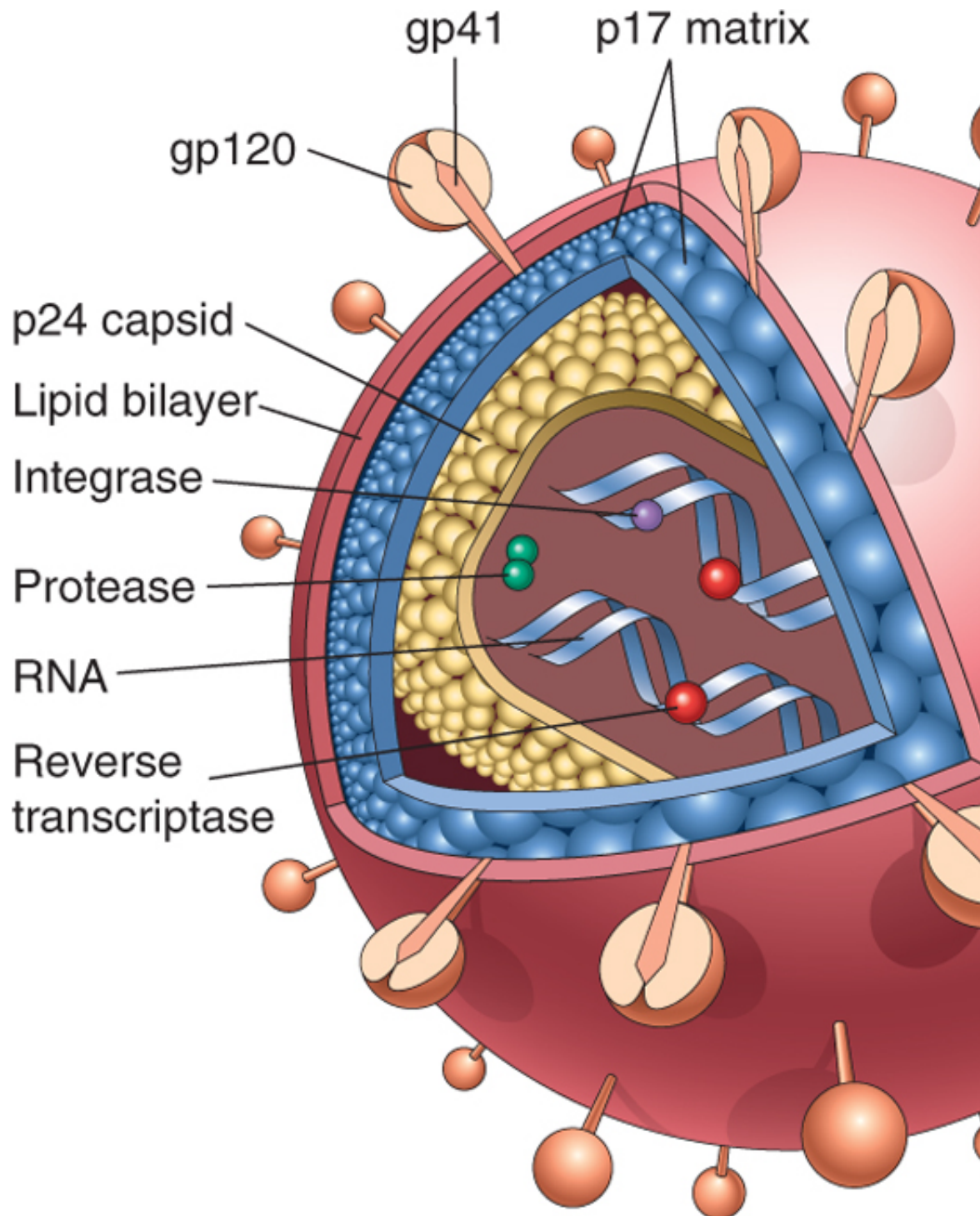
Because of the dismal outcome of AIDS, the lay public is justifiably concerned about the spread of the disease to health care workers. Many of these anxieties can be laid to rest, as extensive studies indicate that *HIV infection is not spread by casual contact in the home, workplace, or school, and no convincing evidence for spread by indirect contact with surfaces or objects*. There is an extremely small but definite risk for transmission of HIV infection to health care workers. Seroconversion after accidental needle-stick injury or exposure of nonintact skin to infected blood in laboratory accidents has been reported. By comparison, the rate of seroconversion after accidental exposure to hepatitis B-infected blood is about 30%. Transmission of HIV from an infected health care worker to a patient is extremely rare.

### *Etiology*

AIDS is caused by HIV, a human retrovirus belonging to the lentivirus family (which also includes immunodeficiency virus, visna virus of sheep, and the equine infectious anemia virus). Two genetic strains of HIV have been identified: HIV-1 and HIV-2. HIV-1 is the cause of the vast majority of AIDS cases.

forms of HIV, called *HIV-1* and *HIV-2*, have been isolated from patients with AIDS. HIV-1 is the most common form in the United States, Europe, and Central Africa, whereas HIV-2 causes a similar disease principally in West Africa. Antiretroviral drugs are now available, and blood collected for transfusion is also routinely screened for HIV-2 seropositivity. Testing is primarily to HIV-1 and diseases caused by it, but it is generally applicable to HIV-2 as well.

### **Structure of HIV**



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Figure 5-30 The structure of HIV. The human immune deficiency virus (HIV)-1 virion. The viral particle is covered  
studded with viral glycoproteins gp41 and gp120.



Like most retroviruses, the HIV-1 virion is spherical and contains an electron-dense, cone-shaped derived from the host cell membrane (Fig. 5-30). The virus core contains: (1) major capsid protein two copies of genomic RNA, and (4) three viral enzymes (protease, reverse transcriptase, and integrase) and is therefore the target for the antibodies used to diagnose HIV infection in blood by a matrix protein called *p17*, lying beneath the virion envelope. The viral envelope itself is studded with gp120, critical for HIV infection of cells. The HIV-1 proviral genome contains the *gag*, *pol*, and *env* proteins. The products of the *gag* and *pol* genes are translated initially into large precursor proteins, which are then cleaved by the viral protease to yield the mature proteins. The highly effective anti-HIV-1 protease inhibitor drugs thus block the formation of mature viral proteins.

In addition to these three standard retroviral genes, HIV contains several other genes (given three: *vif*, *vpr*, and *vpu*) that regulate the synthesis and assembly of infectious viral particles. The product of *vif* is critical for virus replication, causing a 1000-fold increase in the transcription of viral genes. The activity of *vif* (affecting T-cell activation, viral replication, and viral infectivity) and reduces surface expression of CD4 on infected cells. The progression of HIV infection in vivo is dependent on *nef*; strains of simian immunodeficiency virus cause AIDS in monkeys at a markedly decreased rate, and humans infected with a *nef*-deficient virus have a lower burden, with AIDS onset at a substantially slower pace than for nonmutant strains. The products of *vif*, *vpr*, and *vpu* are critical for HIV pathogenicity, and several therapeutic approaches are being developed to block their activity.

Molecular analysis of different viral isolates reveals considerable variability in many parts of the HIV genome. The relatively low fidelity of the viral polymerase, with estimates of one mistake for each  $10^5$  replicated nucleotides, and variability in certain regions of the envelope glycoproteins. Because the immune response against HIV-1 is targeted at these regions, this variability in antigen structure poses a formidable barrier for vaccine development.

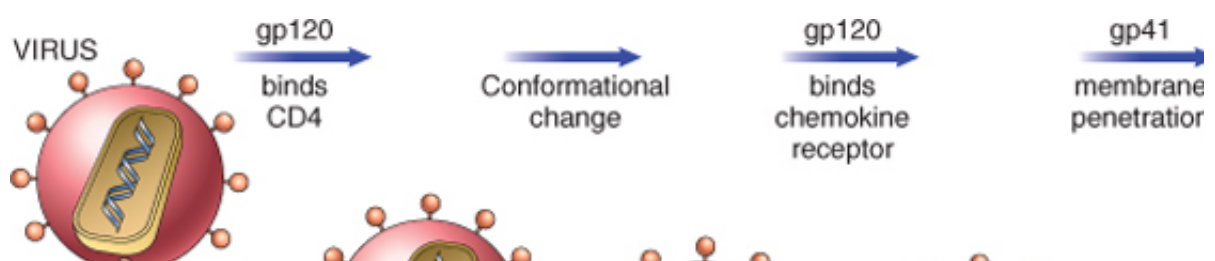
On the basis of the molecular analysis, HIV-1 can be divided into two groups, designated *M* (major) and *O* (outlier). The *M* group, more common form worldwide, are further divided into subtypes (also called *clades*), designated *A* through *N*, based on geographic distribution, with B being the most common form in Western Europe and the United States. The *O* group is found predominantly in Thailand. Beyond molecular homologies, the clades also show differences in modes of transmission. The *B* clade virus grows poorly in DCs and may be transmitted by monocytes and lymphocytes.

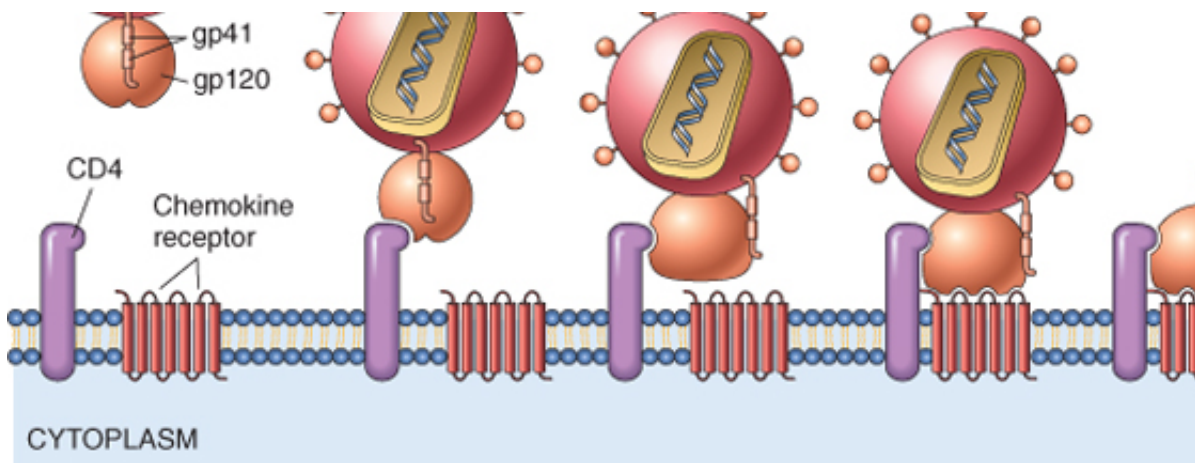
### Pathogenesis

The two major targets of HIV infection are the immune system and the CNS. The life cycle of the virus involves several key interactions with the immune system.

#### Life Cycle of HIV

The entry of HIV into cells requires the CD4 molecule, which acts as a high-affinity receptor for the virus. However, binding of the virus to CD4 is not sufficient for infection; the HIV envelope gp120 must also bind to other cell surface molecules. Two cell surface chemokine receptors, CCR5 and CXCR4, serve this role. HIV envelope gp120 (in association with gp41) binds initially to CD4 molecules (see Fig. 5-31). This binding leads to a conformational change in gp120 for the CXCR4 (mostly on T cells) or CCR5 (mostly on macrophages) coreceptors. The change that allows it to insert into the target membrane, and this process facilitates fusion of the viral envelope with the cell membrane, allowing the core containing the HIV genome to enter the cytoplasm of the cell.





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 Figure 5-31 Molecular basis of HIV entry into host cells. Interactions with CD4 and a chemokine receptor ("coreceptor") are required for HIV entry. The viral envelope fuses with the host cell membrane, allowing the viral genome to enter the cytoplasm. Publishers Ltd, from Wain-Hobson S: HIV. One on one meets two. Nature 384:117

The coreceptors are critical components of the HIV infection process, and their discovery resolved observations regarding HIV tropism. It had been known that HIV strains could be classified according to their ability to infect macrophages and/or CD4<sup>+</sup> T cells. Macrophage-tropic (R5 virus) strains infect both monocytes/macrophages and peripheral blood T cells, whereas T-cell tropic (X4 virus) strains infect only activated T cell lines. This is due to selective coreceptor usage. R5 strains use CCR5 as their coreceptor, and, because CCR5 is expressed on both macrophages and T cells, these cells succumb to infection by R5 strains. Conversely, X4 strains bind to CXCR4, which is expressed only on activated T cells (not on macrophages), so that only activated T cells are susceptible. Interestingly, approximately 80% of HIV is transmitted by R5 strains. However, over the course of infection, X4 viruses gradually accumulate and become the dominant strain responsible for T-cell depletion in the final rapid phase of disease progression. It is thought that dual-tropic strains evolve into X4 strains, as a result of mutations in genes that encode gp120. Individuals with the CCR5-Δ32 mutation (about 20% of whites, 20% are heterozygous and 1% are homozygous for the mutant CCR5) are relatively resistant to HIV infection. Because of the significance of HIV-coreceptor interaction in the pathogenesis of AIDS, this interaction may be of significant therapeutic importance.

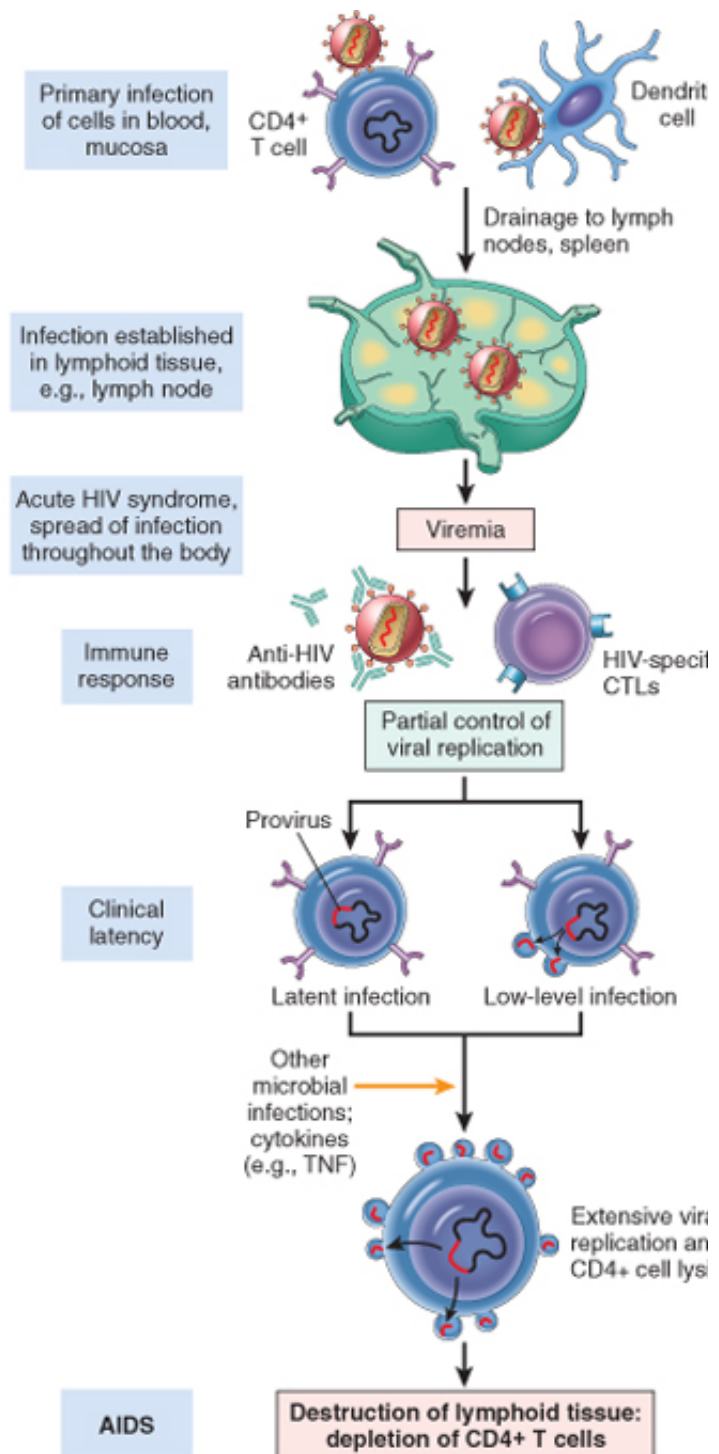
Once internalized, the viral genome undergoes reverse transcription, leading to formation of proviral DNA. In nondividing cells, HIV proviral cDNA may remain in the cytoplasm in a linear episomal form. However, in dividing cells, the provirus becomes integrated into the host genome. After integration, the provirus may remain nontranscribed (latent); alternatively, proviral DNA may be transcribed to form complete viral particles. Such productive infections, associated with extensive viral budding, lead to cell death. In resting T cells, the initiation of proviral DNA transcription (and hence productive infection) occurs only after exposure to antigens or cytokines. Thus, in a cruel twist, physiologic responses to infections and inflammation can lead to the death of infected T cells.

### Progression of HIV Infection

HIV disease begins with acute infection, which is only partly controlled by the host immune response. The first cell types to be infected may be memory T cells in mucosal lymphoid tissues. Because the mucosal tissues are the largest reservoir of T cells in the body, the death of these cells results in considerable depletion of lymphocytes.

*The transition from the acute phase to a chronic phase of infection is characterized by dissemination of the virus and development of host immune responses.* Dendritic cells in epithelia at sites of virus entry capture and transport the virus to lymph nodes. Once in lymphoid tissues, dendritic cells may pass HIV on to CD4<sup>+</sup> T cells through direct contact. After exposure to HIV, viral replication can be detected in the lymph nodes. This replication leads to the production of viral particles, which are present in the patient's blood, accompanied by an acute HIV syndrome that includes symptoms typical of many viral diseases. The virus disseminates throughout the body and infects dendritic cells in peripheral lymphoid tissues. As the infection proceeds, the immune system mounts a response that leads to the depletion of CD4<sup>+</sup> T cells.

dendritic cells in peripheral lymphoid tissues. As the infection spreads, the immune system mounts immune responses directed at viral antigens. These immune responses partially control the infection, which is reflected by a drop in viremia to low but detectable levels by about 12 weeks after the primary infection.



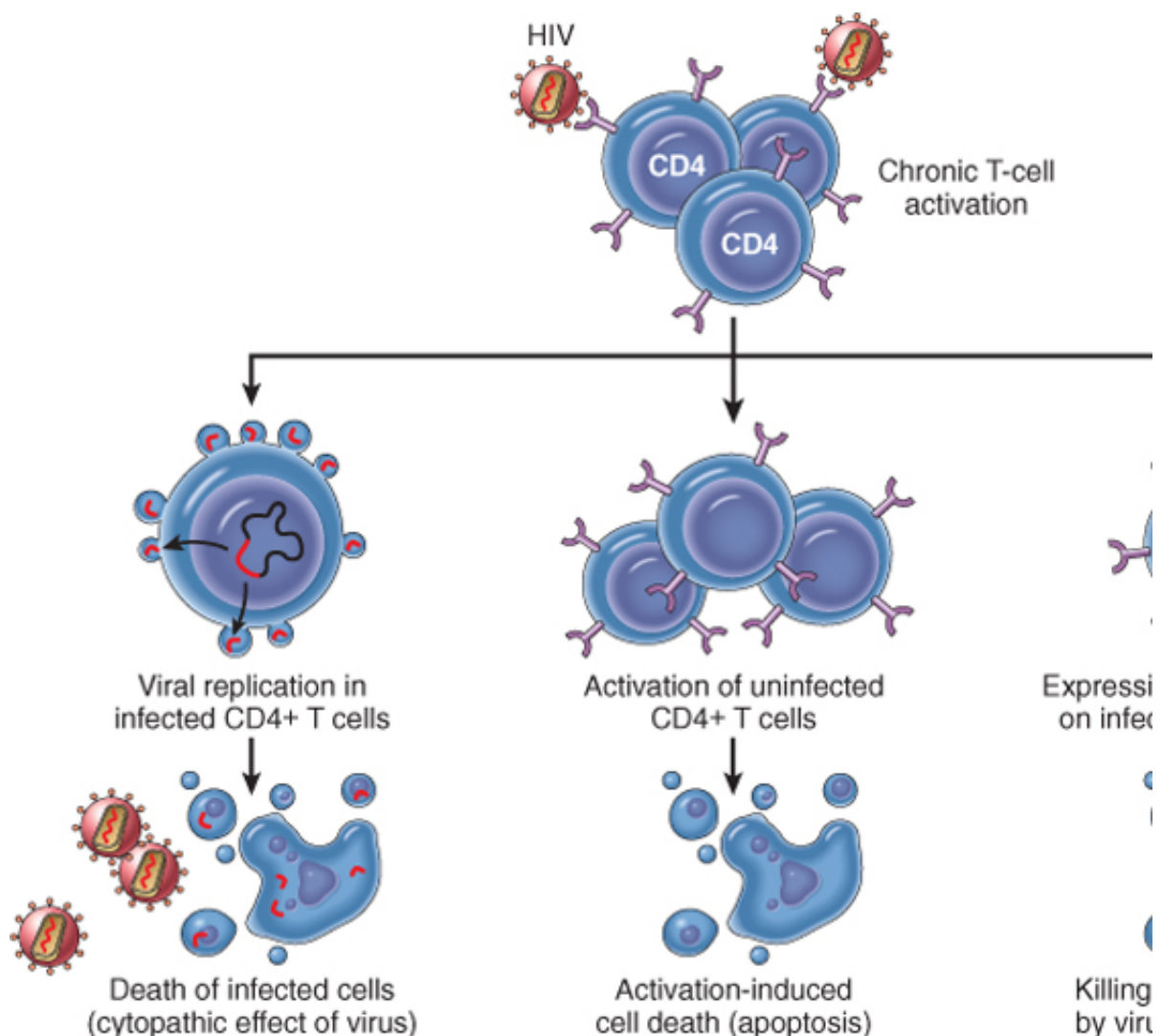
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Figure 5-32 Pathogenesis of HIV infection. Initially, HIV infects T cells and macrophages directly or is carried to the regional lymph nodes, where it leads to viremia and widespread seeding of lymphoid tissue. The viremia is controlled by the immune response, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages is contained, and the number of CD4+ cells declines. There continues a gradual erosion of CD4+ cells by productive infection (or cell death). As cell numbers decline and the patient develops clinical symptoms of full-blown AIDS, macrophages are also parasitized and they transport the virus to tissues, particularly the brain.

In the next, chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV (5-32). During this period of the disease, the immune system remains competent at handling most and few or no clinical manifestations of the HIV infection are present. Therefore, this phase of HIV is called the *latent period*. Although the majority of peripheral blood T cells do not harbor the virus, destruction of CD4+ T cells progresses during the latent period, and the number of circulating blood CD4+ T cells steadily decreases. Approximately  $10^{12}$  T cells are normally found in lymphoid tissues, and it is estimated that HIV destroys approximately 100 million CD4+ T cells every day. Early in the course of the disease, the body may continue to make new CD4+ T cells, and they are replaced almost as quickly as they are destroyed. At this stage, up to 10% of CD4+ T cells in lymphoid tissues may be infected at any one time. Eventually, over a period of years, the continuous cycle of virus infection and T cell death leads to depletion of T cells in the lymphoid tissues and the circulation.

In addition to T-cell depletion, abnormalities have been described in many components of the immune system. Below we describe the major defects in immune cells during the course of HIV infection.

#### Mechanisms of T-cell Depletion in HIV Infection



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Figure 5-33 Mechanisms of CD4 cell loss in HIV infection. Some of the principal known and postulated mechanisms:



**Table 5-10. Major Abnormalities of Immune Function in AIDS**

<b>Lymphopenia</b>
Predominantly caused by selective loss of the CD4 helper T-cell subset; inversion of CD4:CD8 ratio
<b>Decreased T-Cell Function in Vivo</b>
Preferential loss of activated and memory T cells
Decreased delayed-type hypersensitivity
Susceptibility to opportunistic infections
Susceptibility to neoplasms
<b>Altered T-Cell Function in Vitro</b>
Decreased proliferative response to mitogens, alloantigens, and soluble antigens
Decreased cytotoxicity
Decreased helper function for B-cell antibody production
Decreased IL-2 AND IFN- $\gamma$ production
<b>Altered Monocyte or Macrophage Functions</b>
Decreased chemotaxis and phagocytosis
Decreased HLA class II antigen expression
Diminished capacity to present antigen to T cells
Increased spontaneous secretion of IL-1, TNF, IL-6
<b>Polyclonal B-Cell Activation</b>
Hypergammaglobulinemia and circulating immune complexes
Inability to mount de novo antibody response to a new antigen
Poor responses to normal signals for B-cell activation in vitro

IFN- $\gamma$ , interferon- $\gamma$ ; IL-1, interleukin-1; TNF, tumor necrosis factor.

*The major mechanism of loss of CD4<sup>+</sup> T cells is lytic HIV infection of the cells, and cell death during viremia (Fig. 5-33).* Like other cytopathic viruses, HIV disrupts cellular functions sufficiently to cause direct cell lysis, other mechanisms may cause T-cell loss:

Loss of immature precursors of CD4<sup>+</sup> T cells, either by direct infection of thymic progenitor that secrete cytokines essential for CD4<sup>+</sup> T-cell maturation. The result is decreased production of CD4<sup>+</sup> T cells. The result is decreased production of CD4<sup>+</sup> T cells. The result is decreased production of CD4<sup>+</sup> T cells. Because of this "activation-induced death" of uninfected cells, the numbers of T cells that circulate are reduced. Infection of various cells in lymphoid tissues may disrupt the normal immune responses. Fusion of infected and uninfected cells causes formation of syncytia (giant cells). Syncytia formation on productively infected cells binds to CD4 molecules on uninfected T cells, followed by cell death within a few hours. This property of syncytia formation is confined to the X4 strain of HIV. Uninfected T cells lose the CD4 molecule, leading to aberrant signaling and apoptosis. Infected CD4<sup>+</sup> T cells may

The loss of CD4<sup>+</sup> cells leads to an inversion of the CD4:CD8 ratio in the peripheral blood. Thus, normally, the ratio is 2, patients with AIDS have a ratio of 0.5. Such inversion is a common finding in AIDS, but it may also occur in other conditions and therefore not diagnostic.

Although marked reduction in CD4<sup>+</sup> T cells is a hallmark of AIDS and can account for much of the immunodeficiency in HIV infection, there is also compelling evidence for *qualitative defects in T-cell function that can be found in infected persons*. Such defects include reduced antigen-induced T-cell proliferation, impaired T<sub>H</sub>1 intracellular signaling. There is also a selective loss of memory CD4<sup>+</sup> T cells early in the course of infection and a higher level of CCR5 expression in this T-cell subset.

*Low-level chronic or latent infection of T cells (and macrophages)* is an important feature of HIV infection. HIV-infected T cells express infectious virus early in the course of infection, up to 30% of lymph node T cells can be detected. HIV genome. It is widely believed that integrated provirus, without virus production (*latent infection*), can persist for years. Even with highly active antiretroviral therapy (which can eliminate most of the virus in the blood), HIV-infected T cells (as many as 0.05% of resting, long-lived CD4<sup>+</sup> T cells are infected). *Completion of the viral life cycle and cell activation.* Thus, if latently infected CD4<sup>+</sup> cells are activated by environmental antigens, an increase in proviral DNA transcription. This leads to virion production and, in the case of T cells, also results in increased production of cytokines. Responses produced by activated macrophages during normal immune responses can also lead to increased HIV production. Thus, it seems that HIV thrives when the host macrophages and T cells are physiologically activated (e.g., by other microbial agents). The life styles of most HIV-infected patients in the United States place them at high risk for exposure to other sexually transmitted diseases; in Africa, socioeconomic conditions probably increase the risk of HIV infections. It is easy to understand how AIDS patients develop a vicious cycle of T-cell destruction and HIV production because of diminished helper T-cell function lead to increased production of proinflammatory cytokines, which drive more HIV production, followed by infection and loss of additional CD4<sup>+</sup> T cells.

### *Monocytes/Macrophages in HIV Infection*

In addition to infection of CD4<sup>+</sup> T cells, infection of monocytes and macrophages is also extremely important in the course of HIV disease. Similar to T cells, most of the HIV-infected macrophages are found in the tissues and not in the blood. Up to 50% of macrophages in certain tissues, such as brain and lungs, may be infected. Several additional points warrant emphasis:

Although cell division is required for integration and subsequent replication of most retroviruses, terminally differentiated nondividing macrophages, a property conferred by the HIV-1 *vpr* gene, can harbor small amounts of virus from the cell surface but contain large numbers of virus particles located in the cytoplasm. Unlike CD4<sup>+</sup> T cells, macrophages are quite resistant to the cytopathic effects of HIV and can, therefore, survive for long periods. In more than 90% of cases, HIV infection is transmitted by R5 strains. The more virulent R5 strains of HIV are more efficient in transmitting HIV. This suggests that the initial infection is primarily by macrophages for HIV transmission.

Thus, in all likelihood, macrophages are the gatekeepers of HIV infection. Besides providing a portal of entry, macrophages are viral reservoirs and factories, whose output remains largely protected from host immune responses. They provide a vehicle for HIV transport to various parts of the body, particularly the nervous system. If CD4<sup>+</sup> T-cell numbers are massively depleted, macrophages remain a major site of continued viral replication. Although the number of infected monocytes in the circulation is low, their functional deficits (e.g., impaired microbicidal activity, impaired cytokine production, and diminished antigen presentation capacity) have important bearing on host immune responses.

### *DCs in HIV Infection*

In addition to macrophages, two types of DCs are also important targets for the initiation and maintenance of HIV infection: follicular DCs. As discussed earlier, DCs in mucosal epithelia capture the virus and transport it to lymph nodes where T cells are infected. Follicular DCs in the germinal centers of lymph nodes are important reservoirs of HIV. If infected by HIV, most virus particles are found on the surface of their dendritic processes, including those associated with antibody complexes. The antibody-coated virions localized to follicular DCs retain the ability to infect T cells. Macrophages and DCs may also impair the functions of these cell populations, with secondary effects on the immune response.

### *B Cells and Other Lymphocytes in HIV Infection*

Although much attention has been focused on T cells and macrophages, patients with AIDS also have defects in B-cell function. Paradoxically, these patients have hypergammaglobulinemia and circulating immune complexes. B-cell activation. This may result from multiple factors, including infection with CMV or EBV, both of which can drive B-cell activation. HIV gp41 itself can promote B-cell growth and differentiation, and HIV-infected macrophages produce factors that drive B-cell activation. Despite the presence of spontaneously activated B cells, patients with AIDS have impaired humoral responses to newly encountered antigens. Not only is this attributable to deficient T-cell help, but also because independent antigens are also suppressed, suggesting additional B-cell defects. Impaired humoral responses are particularly evident in response to encapsulated bacteria (e.g., *S. pneumoniae* and *H. influenzae*) that require antibody for clearance.

...response to encapsulated bacteria (e.g., *S. pneumoniae* and *H. influenzae*), which require antibody clearance.

CD4<sup>+</sup> T cells play a pivotal role in regulating the immune response: they produce a plethora of cytokines and hematopoietic growth factors (e.g., granulocyte-macrophage colony-stimulating factor). Therefore, they have profound effects on virtually every other cell of the immune system, as summarized in [Table 5-10](#).

### *Pathogenesis of CNS Involvement*

The pathogenesis of the neurologic manifestations in AIDS deserves special mention because, in the nervous system, the brain is a major target of HIV infection. Macrophages and cells belonging to the mononuclear phagocyte system are the predominant cell types in the brain that are infected with HIV. The virus is most likely carried to the brain (thus, brain HIV isolates are almost exclusively of the R5 type). The mechanism of HIV-induced damage is obscure. Because neurons are not infected by HIV, and the extent of neuropathologic changes is proportional to the severity of neurologic symptoms, most experts believe that the neurologic deficit is caused indirectly by factors (e.g., cytokines such as TNF) produced by macrophages/microglia. In addition, nitric oxide-mediated direct damage of neurons by soluble HIV gp120 has been postulated.

## **SUMMARY**

### **HIV Life Cycle and the Pathogenesis of AIDS**

**Virus entry into cells:** requires CD4 and co-receptors, which are receptors for the binding of viral gp120 and fusion with the cell mediated by viral gp41 protein.  
**CD4<sup>+</sup> helper T cells, macrophages, and DCs:** target cells for infection.  
**Viral replication:** provirus genome integration; viral gene expression is triggered by stimuli that activate infected cells (e.g., cytokines produced during normal immune responses).  
**Progression of infection:** infection of mucosal T cells and DCs; viremia with dissemination of virus; latent infection in T cells; continuing viral replication and progressive loss of CD4<sup>+</sup> T cells.  
**Immunodeficiency:**

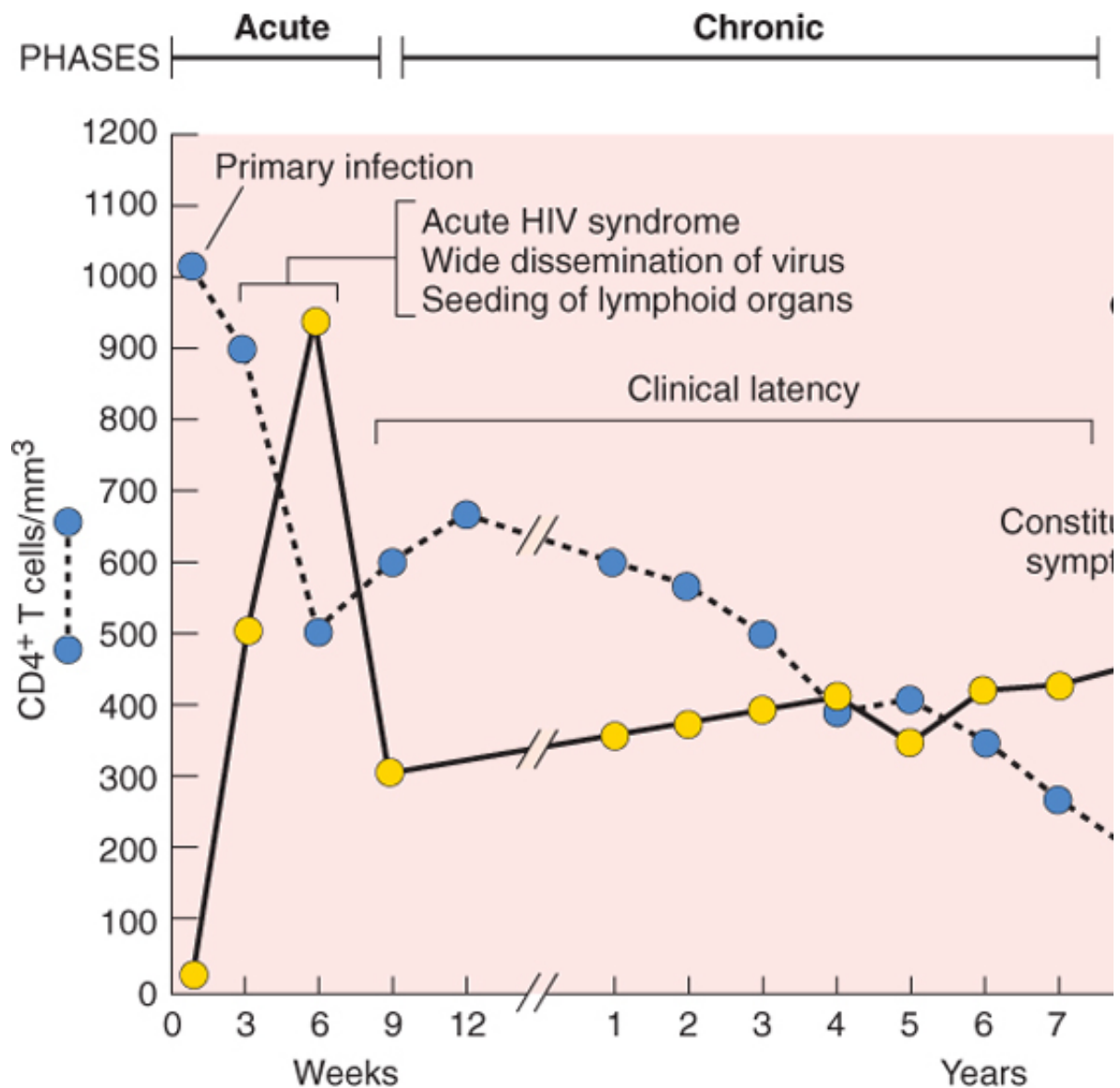
Loss of CD4<sup>+</sup> T cells: T-cell death during viral replication and budding (cytopathic infections); apoptosis as a result of chronic stimulation; defective T-cell functions.  
Defective macrophage and DC functions.  
Destruction of lymphoid tissues (late).

### **Natural History of HIV Infection**

The clinical course of HIV infection can best be understood in terms of an interplay between HIV infection and the host immune response. The dynamics of virus-host interaction can be recognized: (1) an early *acute phase*, (2) a *chronic phase*, and (3) a *late phase* (Fig. 5-34).

The *acute phase* represents the initial response of an immunocompetent adult to HIV infection. It is a self-limited illness that develops in 50% to 70% of adults 3 to 6 weeks after infection; it is characterized by symptoms including sore throat, myalgia, fever, rash, and sometimes aseptic meningitis. This phase is characterized by virus production, viremia, and widespread seeding of the peripheral lymphoid tissues, typical of primary infection. Soon, however, a virus-specific immune response develops, evidenced by seroconversion (antibody exposure) and by the development of virus-specific CD8<sup>+</sup> CTLs. As viremia abates, CD4<sup>+</sup> T cells begin to recover. However, the reduction in plasma virus does not signal the end of viral replication, which continues at a low level in macrophages in the tissues (particularly lymphoid organs). The middle, *chronic phase* represents a period of persistent infection. The immune system is largely intact at this point, but there is *continued HIV replication*. Patients either are asymptomatic or develop persistent lymphadenopathy, and many patients develop opportunistic infections such as thrush (*Candida*) or herpes zoster. During this phase, viral replication in the lymphoid tissues is extensive; viral turnover is associated with continued loss of CD4<sup>+</sup> cells, but a large proportion of the decline of CD4<sup>+</sup> cells in the peripheral blood is modest. After an extended and variable period of relative stability, the proportion of the surviving CD4<sup>+</sup> cells infected with HIV increases, and host immune function declines. The late phase of infection is characterized by significant constitutional symptoms (fever, rash, fatigue) that reflect the

decompensation, escalation of viral replication, and the onset of the "crisis" phase. The final catastrophic breakdown of host defenses, a marked increase in viremia, and clinical disease of more than 1 month's duration, fatigue, weight loss, and diarrhea; the CD4+ cell count is variable interval, patients develop serious opportunistic infections, secondary neoplasms, and are called *AIDS-defining conditions*, and the patient is said to have full-blown AIDS. Even if they do not manifest, Centers for Disease Control (CDC) guidelines define any HIV-infected individual with a CD4+ cell count below 200 per microliter as having AIDS.



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 Figure 5-34 Clinical course of HIV infection. During the early period after primary infection, there is widespread dissemination of virus and a decrease in the number of CD4+ T cells in peripheral blood. An immune response to HIV ensues, with a decrease in viremia following. During this period, viral replication continues. The CD4+ T-cell count gradually decreases during the subsequent years, and there is a substantial risk of opportunistic diseases. (Redrawn from Fauci AS, Lane HC: Human immunodeficiency virus infection. In: Fauci AS, et al (eds): Harrison's Principles of Internal Medicine, 14th ed. New York, McGraw-Hill, 1997, p 1791. From Elsevier Publishing Companies.)

In the absence of treatment, most patients with HIV infection develop AIDS after a chronic phase. Patients are divided into *rapid progressors* and long-term *nonprogressors*. In rapid progressors, the middle, chronic phase is short, and the final, catastrophic phase is long. Nonprogressors (fewer than 5% of infected persons) are defined as HIV-infected



primary infection. Nonprogressors (fewer than 5% of infected persons) are defined as HIV-infected for 10 years or more, with stable CD4<sup>+</sup> counts and low levels of plasma viremia; notably, AIDS even patients, albeit after a much prolonged clinical latency. Despite much study, the reason for nonpro

Because the loss of immune containment is associated with declining CD4<sup>+</sup> T-cell counts, the CD patients into three categories on the basis of CD4<sup>+</sup> T-cell counts: more than 500 cells/ $\mu$ L, between cells/ $\mu$ L. Patients in the first group are generally asymptomatic; counts below 500 cells/ $\mu$ L are associated decline of CD4<sup>+</sup> T-cell levels below 200 cells/ $\mu$ L is associated with severe immunosuppression. For are an important adjunct to HIV viral load measurements. The significance of these two measures whereas CD4<sup>+</sup> cell counts indicate the status of the patient's disease at the time of measurement the direction in which the disease is progressing.

It should be evident from our discussion that in each of the three phases of HIV infection viral replication rate. Even in the middle, chronic phase, before the severe decline in the CD4<sup>+</sup> cell count, there is, in words, *HIV infection lacks a phase of true microbiologic latency*, that is, a phase during which *all* T no cell is productively infected. Multiple-drug antiretroviral therapy has dramatically slowed the progression frequency of opportunistic infections and other complications. However, the available therapy does disease can recur if treatment is stopped. It is also not known if drug-resistant viral strains will become

### Clinical Features

The clinical manifestations of HIV infection range from a mild acute illness to severe disease. Because acute, early and chronic, middle phases of HIV infection were described earlier, only the clinical manifestations of blown AIDS, are summarized here.

In the United States the typical adult patient with AIDS presents with fever, weight loss, diarrhea, recurrent opportunistic infections, neurologic disease, and (in many cases) secondary neoplasms. The infections are included in the surveillance definition of AIDS.

### Opportunistic Infections

**Table 5-11. AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with**

Infections
<b>PROTOZOAL AND HELMINTHIC INFECTIONS</b>
Cryptosporidiosis or isosporidiosis (enteritis)
Pneumocystosis (pneumonia or disseminated infection)
Toxoplasmosis (pneumonia or CNS infection)
<b>FUNGAL INFECTIONS</b>
Candidiasis (esophageal, tracheal, or pulmonary)
Cryptococcosis (CNS infection)
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)
<b>BACTERIAL INFECTIONS</b>
Mycobacteriosis ("atypical," e.g., <i>Mycobacterium avium-intracellulare</i> , disseminated or extrapulmonary; <i>M. tuberculosis</i> extrapulmonary)
Nocardiosis (pneumonia, meningitis, disseminated)
<i>Salmonella</i> infections, disseminated
<b>VIRAL INFECTIONS</b>
Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)
Herpes simplex virus (localized or disseminated)
Varicella-zoster virus (localized or disseminated)
Progressive multifocal leukoencephalopathy
<b>Neoplasms</b>

Kaposi sarcoma
Non-Hodgkin lymphomas (Burkitt, immunoblastic)
Primary lymphoma of brain
Invasive cancer of uterine cervix

CNS, central nervous system.

Opportunistic infections have accounted for approximately 80% of deaths in patients with AIDS. Their incidence is decreasing markedly as a result of more effective highly active antiretroviral therapy. A list of opportunistic infections is provided here.

Pneumonia caused by the opportunistic fungus *Pneumocystis jirovecii* (representing reactivation of latent infection) is a presenting feature in many cases, although its incidence is declining as a result of effective prophylaxis. This infection is extremely high in individuals with fewer than 200 CD4<sup>+</sup> T cells/ $\mu$ L. Many patients have other than *P. jirovecii* pneumonia (see [Table 5-11](#)). Among the most common are recurrent mucocutaneous infection (particularly enteritis and retinitis), severe ulcerating oral and perianal herpes simplex, and *tuberculosis* and atypical mycobacteria (*Mycobacterium avium-intracellulare*). The AIDS epidemic in the United States. Although in most cases it represents reactivation, the frequency of *M. tuberculosis* manifests itself early in the course of AIDS, infections with atypical mycobacteria are common in HIV disease, usually occurring in patients with fewer than 100 CD4<sup>+</sup> cells/ $\mu$ L. Toxoplasmosis is the most common CNS infection. Cryptococcal meningitis is also quite frequent. Persistent diarrhea, which is common in patients with *Cryptosporidium* or *Isospora belli* infections, but bacterial pathogens such as *Salmonella* species are also involved. Because of depressed humoral immunity, AIDS patients are susceptible to infections with

### Neoplasms

Patients with AIDS have a high incidence of certain tumors, particularly Kaposi sarcoma (KS), non-Hodgkin lymphomas, and cancer of the cervix. The basis of the increased risk of malignancy is multifactorial: profound defects in cellular and monocyte functions, and multiple infections with known (e.g., human herpesvirus type 8, EBV virus).

KS, a vascular tumor that is otherwise rare in the United States ([Chapter 10](#)), is the most common tumor in AIDS patients (its incidence has decreased significantly with anti-retroviral therapy). The tumor is far more common in intravenous drug abusers or patients belonging to other risk groups. The lesions can arise in immunocompetent individuals, or in advanced stages of HIV infection. Unlike the lesions in sporadic cases of KS, the lesions in AIDS are multicentric and tend to be more aggressive; they can affect the skin, mucous membranes, gastrointestinal tract, and other organs. The lesions contain spindle cells that share features with endothelial cells and smooth muscle cells. The lesions are composed of endothelial cells or mesenchymal cells that can form vascular channels. In different patients, the lesions are monoclonal or polyclonal, indicating that KS is not always a typical tumor.

KS is caused by a herpesvirus called Kaposi sarcoma herpesvirus (KSHV) or human herpesvirus-8. Infection with this virus is necessary for the development of KS, but the mechanism by which KSHV infection leads to the vascular lesions is unknown. One hypothesis is that KSHV infects endothelial cells in concert with cytokines produced by HIV-infected immune cells, stimulates proliferation of the virus, and promotes expression of homologues of several human genes known to affect cellular survival and proliferation. Why the prevalence of KS is higher in AIDS patients is unclear.

*Non-Hodgkin lymphomas* constitute the second most common type of AIDS-associated tumors. They occur most frequently in severely immunosuppressed patients, and involve many extranodal sites. The lymphomas are often of the B-cell type, and hence primary lymphoma of the brain is considered an AIDS-defining condition. In keeping with this, most such lymphomas have a diffuse large-cell histologic picture ([Chapter 12](#)). As with the majority of cancers that occur in the setting of AIDS are primarily of B-cell origin. At least in some cases (30% to 40%) the lymphomas are associated with EBV infection and progress from polyclonal to monoclonal B-cell lesions. Another less common AIDS-related tumor is primary CNS lymphoma, which is also associated with KSHV infection; it grows exclusively in body cavities in the form of nodules or diffuse infiltrations.

*Cervical carcinoma* is also increased in patients with AIDS. This is attributable to a high prevalence of human papillomavirus infection.

Cervical carcinoma is also increased in patients with AIDS. This is attributable to a high prevalence in patients with AIDS whose immune systems are compromised. This virus is believed to be intimately associated with carcinoma of the cervix and its precursor lesions, cervical dysplasia and carcinoma in situ ([Chapter 23](#)). It should be part of the routine evaluation of HIV-infected women.

### *CNS Involvement*

Involvement of the CNS is a common and important manifestation of AIDS. At autopsy 90% of patients have CNS involvement, and 40% to 60% have clinically evident neurologic dysfunction. Significantly, in some cases, CNS involvement may be the sole or earliest presenting feature of HIV infection. In addition to opportunistic infections and neurodegenerative changes, various neuropathologic changes occur. These include an aseptic meningitis occurring at the time of seroconversion, peripheral neuropathies, and (most commonly) a progressive encephalopathy clinically designated as [Chapter 23](#).

### **Morphology**

The anatomic changes in the tissues (with the exception of lesions in the brain) are diagnostic. In general, the pathologic features of AIDS are those of widespread opportunistic infections and lymphoid tumors. Most of these lesions are discussed elsewhere, because they are not seen in patients who do not have HIV infection. To appreciate the distinctive nature of lesions in the context of other disorders affecting the brain ([Chapter 23](#)). Here the focus is on lymphoid organs.

Biopsy specimens from enlarged lymph nodes in the early stages of HIV infection reveal follicular hyperplasia ([Chapter 12](#)). The medulla contains abundant **plasma cells**. These cells, located in the B-cell areas of the node, are the morphologic counterparts of the polyclonal B-cell hypergammaglobulinemia seen in AIDS patients. In addition to changes in the follicles, there is increased cellularity, due primarily to increased numbers of macrophages but also of lymphoblasts and plasma cells. HIV particles can be demonstrated within the germinal centers and on the villous processes of the follicular DCs. Viral DNA can also be detected in macrophages and T cells.

With disease progression, the frenzy of B-cell proliferation gives way to a pattern of follicular involution and generalized lymphocyte depletion. The organized network of follicles and medullary cords may even become hyalinized. These "burnt-out" lymph nodes are atrophic and do not harbor numerous opportunistic pathogens. Because of profound immunosuppression, the host response to infections both in the lymph nodes and at extranodal sites may be sparse. For example, with severe immunosuppression, mycobacteria do not evoke granuloma formation. CD4<sup>+</sup> T cells are lacking. In the empty-looking lymph nodes and in other organs, the presence of opportunistic infections may not be readily apparent without the application of special stains. As might be expected, lymphocyte depletion is not confined to the nodes; in the later stages of AIDS, the spleen and thymus are also atrophic, and the lungs are "wastelands."

Non-Hodgkin lymphomas, involving the nodes as well as extranodal sites such as the spleen, liver, and bone marrow, are primarily high-grade diffuse B-cell neoplasms ([Chapter 12](#)).

Since the emergence of AIDS in 1981, the concerted efforts of epidemiologists, immunologists, and virologists have led to spectacular advances in our understanding of this disorder. Despite all this progress, however, the prognosis remains poor. Although the mortality rate has begun to decline in the United States as a result of the use of combination antiretroviral drugs, all treated patients still carry viral DNA in their lymphoid tissues. Can there be a cure with present knowledge? An effort has been mounted to develop a vaccine, many hurdles remain to be crossed before vaccine development becomes a reality. Molecular analyses have revealed an alarming degree of variation in viral isolates, making vaccine development even more difficult. A further complication to this task is that the nature of the virus is not fully understood. Consequently, at present, prevention and effective public health measures, combined with antiretroviral therapy, remain the mainstays in the fight against AIDS.







## AMYLOIDOSIS

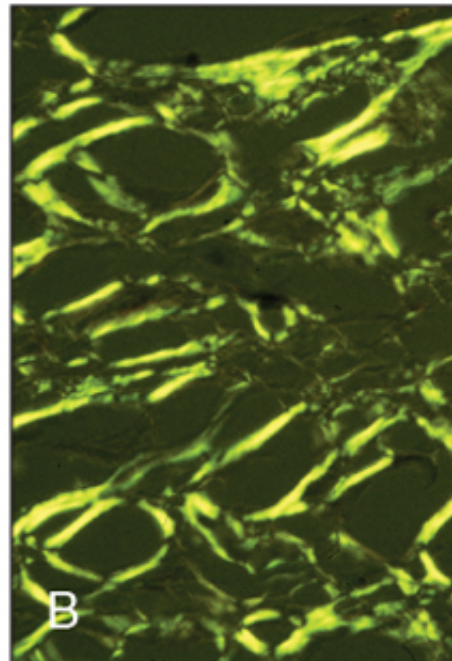
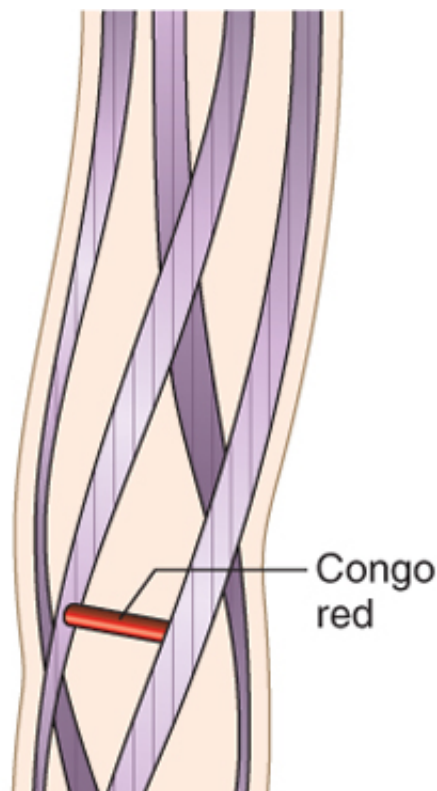
*Amyloidosis* is a condition associated with a number of inherited and inflammatory disorders in which proteins are responsible for tissue damage and functional compromise. These abnormal fibrils are misfolded proteins (which are soluble in their normal folded configuration). The fibrillar deposits bind glycosaminoglycans, including heparan sulfate and dermatan sulfate, and plasma proteins, notably albumin. The presence of abundant charged sugar groups in these adsorbed proteins give the deposits a starchy appearance. They resemble starch (amylose). Therefore, the deposits were called *amyloid*, a name that is firmly entrenched even though the deposits are unrelated to "starch."

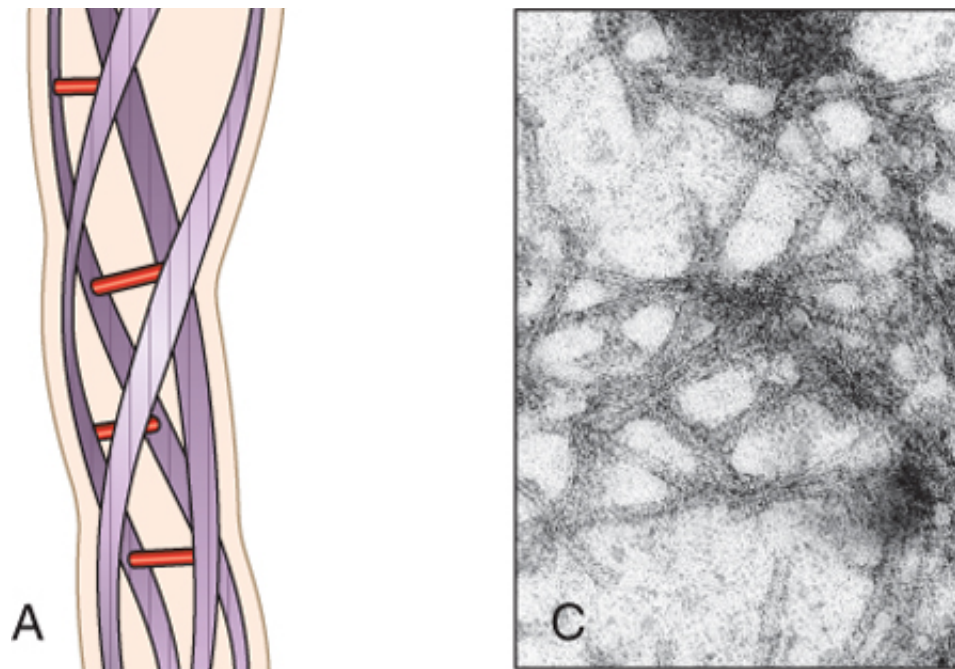
### *Pathogenesis of Amyloid Deposition*

*Amyloidosis is fundamentally a disorder of protein misfolding.* Amyloid is not a structurally homogeneous entity. In fact, more than 20 (at last count, 23) different proteins can aggregate to form amyloid. Regardless of their derivation, all amyloid deposits are composed of nonfibrillar deposits. Each is formed of  $\beta$ -sheet polypeptide chains that are wound together (Fig. 5-35). The dye Congo red binds to the amyloid, giving it a characteristic red-green dichroism (birefringence), which is commonly used to identify amyloid deposits in tissue.

Several factors may contribute to the aggregation of certain proteins and the formation of fibrils (Fig. 5-36).

The protein may have a tendency to form aggregates of misfolded forms but does so only at abnormally high levels. This may happen as an individual ages (senile amyloidosis), or when there are chronic inflammatory states), or if excretion of the protein is impaired (amyloidosis associated with multiple myeloma). A mutation may give rise to a form of a protein that has a tendency to fold improperly and form aggregates. Finally, proteolysis may generate a protein that forms amyloid fibrils (amyloidosis associated with Alzheimer's disease).

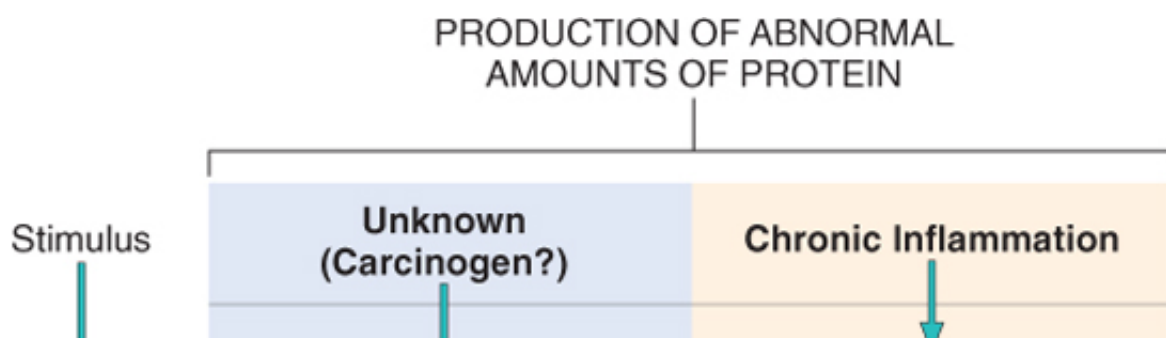


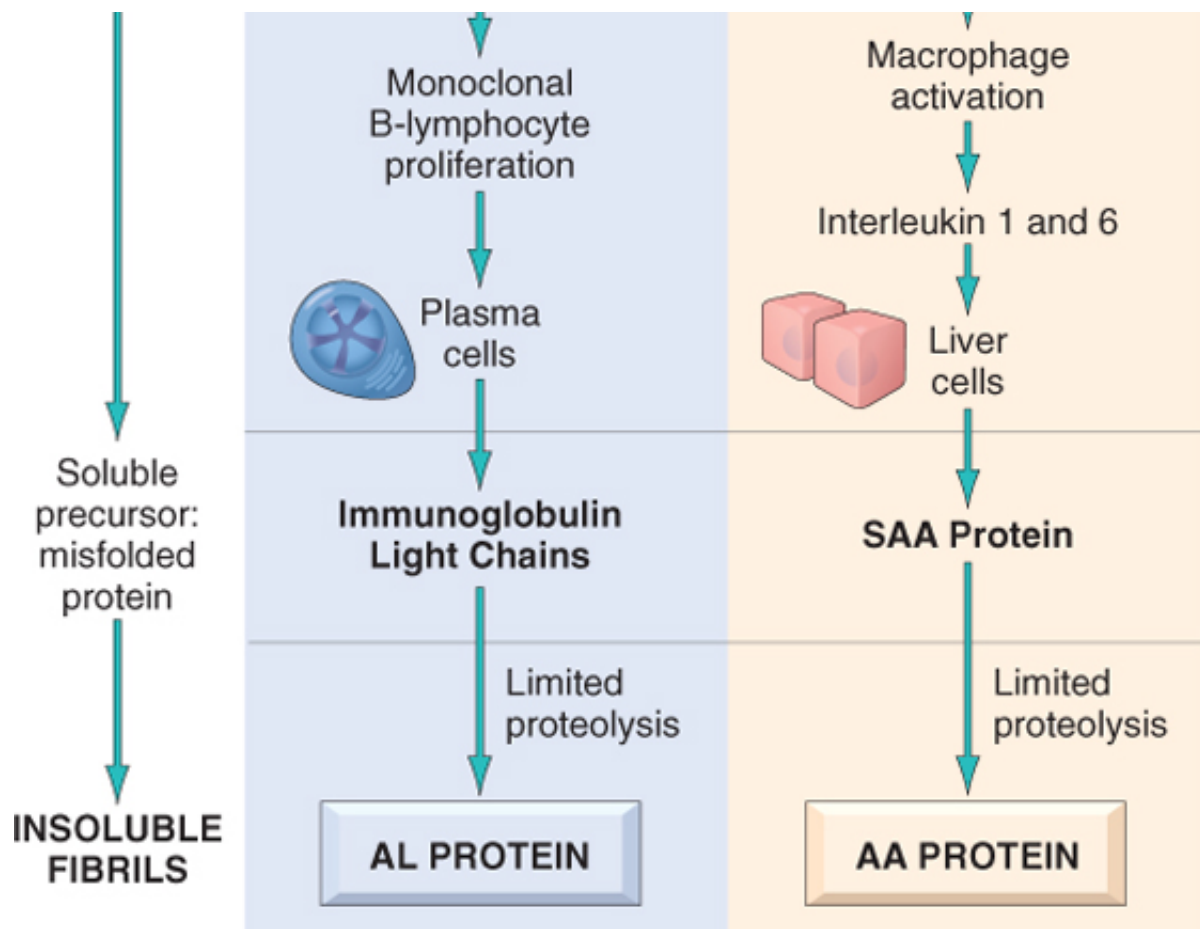


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 Figure 5-35 Structure of amyloid. **A**, Schematic diagram of an amyloid fiber showing fibrils (4 shown, may be up spaced binding of the Congo red dye. **B**, Congo red staining shows an apple-green birefringence under polarized micrograph of 7.5-10 nm amyloid fibrils. (Reproduced from Merlini, G. and Bellotti, V. Molecular mechanisms of ar Copyright 2003 Massachusetts Medical Society. All rights reserved

Of the more than 20 biochemically distinct forms of amyloid proteins that have been identified, the

The **AL (amyloid light chain) protein** is produced by plasma cells and is made up of complete amino-terminal fragments of light chains, or both. Only a few types of Ig light chains are produced because they contain amino acid residues that destabilize the domain structure. As expected, the AL type is associated with some form of monoclonal B-cell proliferation. The **AA (amyloid A) nonimmunoglobulin protein** derived from a larger (12-kD) serum precursor called **SAA (serum AAI synthesized in the liver**. The production of this protein is increased in inflammatory states and therefore this form of amyloidosis is associated with chronic inflammatory disorders. Increased production is sufficient to generate amyloid deposits. It is believed that SAA is normally degraded to soluble fragments by enzymes. Defective proteolysis may produce misfolded, incompletely degraded SAA, leading to amyloid fibrils. Although this is a plausible hypothesis, specific enzymatic defects have not been identified in the cerebral lesions of **Alzheimer disease**. **Aβ** is a 4-kD peptide that constitutes the core of the amyloid deposits in cerebral blood vessels in this disease. The Aβ protein is derived from a much larger **amyloid precursor protein (APP)** (Chapter 23).





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Figure 5-36 Pathogenesis of amyloidosis. The proposed mechanisms underlying deposition of th

Several other proteins have been found in amyloid deposits in a variety of clinical settings:

*Transthyretin* (TTR) is a normal serum protein that binds and transports thyroxine and retin gene encoding transthyretin result in the production of a protein (and its fragments) that ag resultant diseases are called *familial amyloid polyneuropathies*. Transthyretin is also depos (senile systemic amyloidosis); in such cases the protein is structurally normal, but it accum cases of familial amyloidosis are associated with deposits of mutant *lysozyme.β2-microglo* molecules and a normal serum protein, has been identified as the amyloid fibril subunit (Aβ course of patients on *long-term hemodialysis*. Aβ2m fibers are structurally similar to norma high concentrations in the serum of patients with renal disease and is retained in the circul through dialysis membranes. In some series, as many as 60% to 80% of patients on long-t in the synovium, joints, and tendon sheaths. Amyloid deposits derived from diverse precurs keratin have also been reported.

#### Classification of Amyloidosis

Because a given biochemical form of amyloid (e.g., AA) may be associated with amyloid depositic biochemical and clinical classification is followed for this discussion (Table 5-12). Amyloid may be organ systems, or it may be *localized*, when deposits are limited to a single organ, such as the he generalized, pattern is subclassified into *primary amyloidosis* when associated with some immunc when it occurs as a complication of an underlying chronic inflammatory or tissue destructive proce constitutes a separate, albeit heterogeneous group, with several distinctive patterns of organ invo

## Immunocyte Dyscrasias with Amyloidosis (Primary Amyloidosis)

**Table 5-12. Classification of Amyloidosis**

Clinicopathologic Category	Associated Diseases	Major Fibrin Protein
<b>Systemic (Generalized) Amyloidosis</b>		
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal B-cell proliferations	AL
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA
Hemodialysis-associated amyloidosis	Chronic renal failure	A $\beta$ <sub>2</sub> m
<b>Hereditary Amyloidosis</b>		
Familial Mediterranean fever		AA
Familial amyloidotic neuropathies (several types)		ATTR
Senile Amyloidosis		ATTR
<b>Localized Amyloidosis</b>		
Senile cerebral	Alzheimer disease	A $\beta$
Endocrine		
Medullary carcinoma of thyroid		A Cal
Islets of Langerhans	Type 2 diabetes	AIAPP
Isolated atrial amyloidosis		AANF

Amyloid in this category is usually systemic in distribution and is of the AL type. With approximate United States, this is the most common form of amyloidosis. The best example in this category is *myeloma*, a malignant neoplasm of plasma cells ([Chapter 12](#)). The malignant B cells characteristic single specific Ig (monoclonal gammopathy), producing an M (myeloma) protein spike on serum electrophoresis of whole Ig molecules, plasma cells may also synthesize and secrete either the  $\gamma$  or  $\kappa$  light chain proteins (by virtue of the small molecular size of the Bence Jones proteins, they are also frequently present in the serum of as many as 70% of patients with multiple myeloma, and almost all patients have Bence Jones proteins in the serum or urine, or both. However, only 6% to 15% of myeloma patients develop amyloidosis. Clearly, the presence of Bence Jones proteins, though necessary, is by itself insufficient. Other variables, such as the type of light chain produced and its catabolism, contribute to the amount of amyloid deposition of Bence Jones proteins.

The great majority of patients with AL amyloid do not have classic multiple myeloma or any other associated disease, nevertheless classified as primary amyloidosis because their clinical features derive from the effect of the abnormal protein. In virtually all such cases, patients have a modest increase in the number of plasma cells and monoclonal immunoglobulins or free light chains can be found in the serum or urine. Clearly, this is a dyscrasia in which production of an abnormal protein, rather than production of tumor masses, is the primary feature.

### Reactive Systemic Amyloidosis

The amyloid deposits in this pattern are systemic in distribution and are composed of AA protein. It is classified as *secondary amyloidosis*, because it is secondary to an associated inflammatory condition. The most common form of systemic amyloidosis is protracted cell injury occurring in a spectrum of infectious and noninfectious conditions. Classically, tuberculosis, bronchiectasis, and chronic osteomyelitis were the most common causes. With the advent of antimicrobial therapies, reactive systemic amyloidosis is seen most frequently in the setting of chronic inflammatory states (e.g., RA, ankylosing spondylitis, and inflammatory bowel disease). RA is particularly prone to amyloid deposition seen in as many as 3% of such patients. Chronic skin infections caused by "skin-popping" can lead to amyloid deposition. Finally, reactive systemic amyloidosis may also occur in association with tumors, the two most common being renal cell carcinoma and Hodgkin lymphoma.

### Familial (Hereditary) Amyloidosis



### Familial (Hereditary) Amyloidosis

A variety of familial forms of amyloidosis have been described; most are rare and occur in limited geographic areas. The most common is an autosomal recessive condition called *familial Mediterranean fever*. This is a febrile disorder characterized by recurrent attacks of inflammation accompanied by inflammation of serosal surfaces, including peritoneum, pleura, and synovial membranes. It occurs predominantly in individuals of Armenian, Sephardic Jewish, and Arabic origins. It is associated with wide-spread amyloid deposition, indistinguishable from reactive systemic amyloidosis. The amyloid fibril proteins are made up of A $\beta$ 2M. This form of amyloidosis is related to the recurrent bouts of inflammation that characterize this disease. The gene has been cloned, and its product is called *pyrin*; although its exact function is not known, it has been suggested to be involved in regulating acute inflammation, presumably by inhibiting the function of neutrophils. With a mutation, it leads to a vigorous, tissue-damaging inflammatory response.

In contrast to familial Mediterranean fever, a group of autosomal dominant familial disorders is characterized by amyloid deposition predominantly in the peripheral and autonomic nerves. These familial amyloidotic polyneuropathies occur in different parts of the world, for example, in Portugal, Japan, Sweden, and the United States. As most of these familial polyneuropathies are made up of mutant ATTRs.

### Localized Amyloidosis

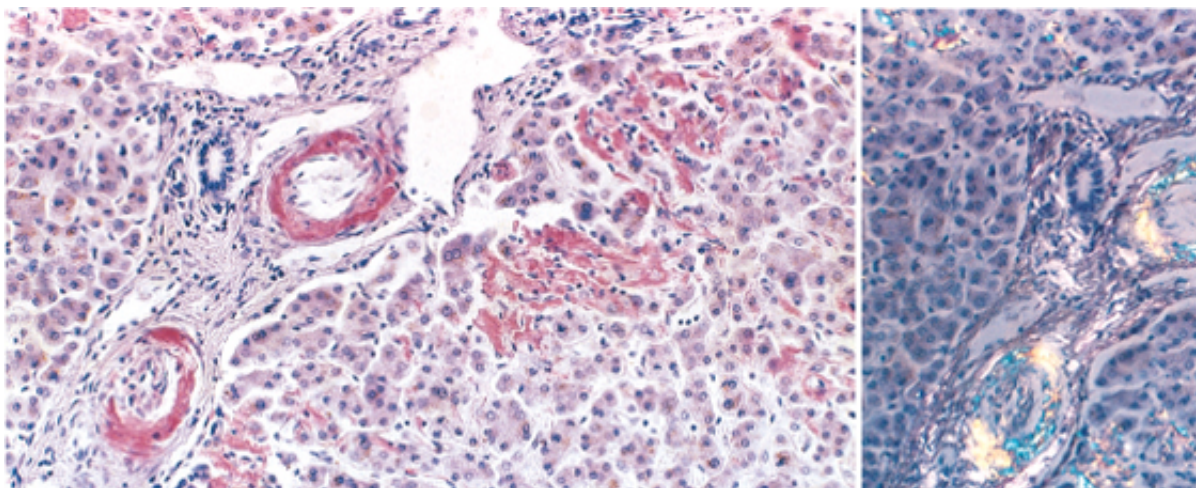
Sometimes amyloid deposits are limited to a single organ or tissue without involvement of any other organs. These localized forms produce grossly detectable nodular masses or be evident only on microscopic examination. Nodules are most often encountered in the lung, larynx, skin, urinary bladder, tongue, and the region about the thyroid gland. They are composed of lymphocytes and plasma cells in the periphery of these amyloid masses, raising the question of whether the immune response to the deposition of amyloid or instead is responsible for it. At least in some cases, the nodules are therefore represent a localized form of immunocyte-derived amyloid.

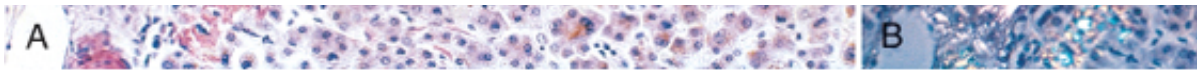
### Endocrine Amyloid

Microscopic deposits of localized amyloid may be found in certain endocrine tumors, such as medullary thyroid carcinoma, islet tumors of the pancreas, pheochromocytomas, and undifferentiated carcinomas of the stomach. In patients with type 2 diabetes mellitus. In these settings, the amyloidogenic proteins seem to be hormones (medullary carcinoma) or from unique proteins (e.g., islet amyloid polypeptide).

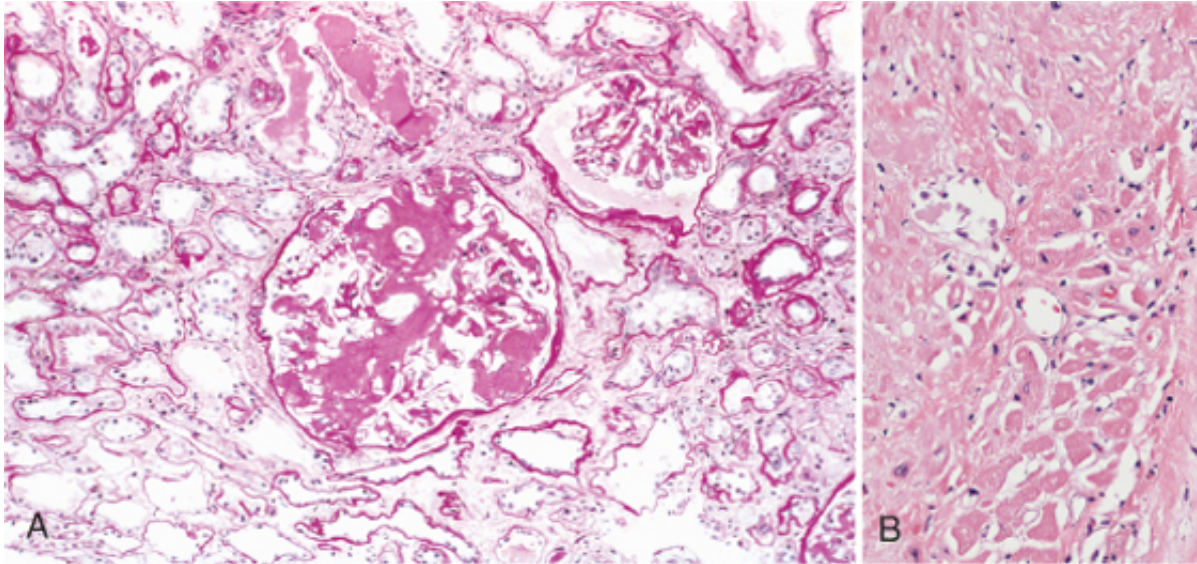
### Amyloid of Aging

Several well-documented forms of amyloid deposition occur with aging. *Senile systemic amyloidosis* is a form of amyloid in elderly patients (usually in their 70s and 80s). Because of the dominant involvement of the heart (typically presenting as a restrictive cardiomyopathy and arrhythmias), this form is also called *senile cardiac amyloidosis*. This form is composed of the normal TTR molecule. In addition, another form predominantly affects the heart, called *senile cardiac amyloidosis*, is composed of deposition of a *mutant form of TTR*. Approximately 4% of the black population in the United States with restrictive cardiomyopathy has been identified in both homozygous and heterozygous patients.





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Figure 5-37 Amyloidosis. **A**, A section of the liver stained with Congo red reveals pink-red deposits of amyloid in the  
Note the yellow-green birefringence of the deposits when observed by polarizing microscope. (Courtesy of Dr. T  
Pathology, University of Texas Southwestern Medical School, Dallas, TX)



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Figure 5-38 Amyloidosis. **A**, Amyloidosis of the kidney. The glomerular architecture is almost totally obliterated by the  
amyloidosis. The atrophic myocardial fibers are separated by structureless, pink-stained amyloid deposits.

### Morphology

There are no consistent or distinctive patterns of organ or tissue distribution of amyloidosis. Nonetheless, a few generalizations can be made. In amyloidosis associated with inflammatory disorders, kidneys, liver, spleen, lymph nodes, adrenals, and thyroid, tissues, are typically affected. Although immunocyte-associated amyloidosis cannot be distinguished from the secondary form by its organ distribution, it more often involves the heart, respiratory tract, peripheral nerves, skin, and tongue. However, the same organs are affected in systemic amyloidosis (secondary amyloidosis), including kidneys, liver, and spleen. Deposits in the immunocyte-associated form of the disease. The localization of amyloidosis in hereditary syndromes is varied. In familial Mediterranean fever the amyloidosis mainly affects the kidneys, blood vessels, spleen, respiratory tract, and (rarely) liver. The localization of remaining hereditary syndromes can be inferred from the designation of these entities.

Whatever the clinical disorder, the amyloidosis may or may not be apparent on macroscopic examination. Often small amounts are not recognized until the surface of the cut organ is painted with 1% picric acid. This yields mahogany brown staining of the amyloid deposits. When amyloidosis is in large amounts, the organ is frequently enlarged and the tissue appears gray with a waxy texture. **Histologically, the amyloid deposition is always extracellular and begins beneath** adjacent to basement membranes. As the amyloid accumulates, it encroaches on and destroys the surrounding and destroying them. In the immunocyte-associated form, perivascular localizations are common.

The histologic diagnosis of amyloid is based almost entirely on its staining characteristics. The commonly used staining technique uses the dye Congo red, which under ordinary light appears pink to amyloid deposits. Under polarized light the Congo red-stained amyloid shows yellow-green birefringence (Fig. 5-37). This reaction is shared by all forms of amyloid and is caused by the pleated configuration of amyloid fibrils. Confirmation can be obtained by electron microscopy.

amorphous nonoriented thin fibrils. AA, AL, and ATTR types of amyloid can also be immunohistochemical staining.

Because the pattern of organ involvement in different clinical forms of amyloidosis major organ involvements is described separately.

**Kidney.** Amyloidosis of the kidney is the most common and most serious involvement. Grossly, the kidney may appear unchanged, or it may be abnormally large, pale, and grossly, in standing cases, the kidney may be reduced in size. Microscopically, the **amyloid deposits are principally in the glomeruli**, but they are also present in the interstitial peritubular walls of the blood vessels. The glomerulus first develops focal deposits within the capillary walls, then diffuse or nodular thickenings of the basement membranes of the capillary loops. As amyloid deposition encroaches on the capillary lumina and eventually leads to total obliteration (Fig. 5-38A). The interstitial peritubular deposits are frequently associated with the pink casts within the tubular lumens, presumably of a proteinaceous nature. Amyloid deposits in the walls of blood vessels of all sizes, often causing marked vascular narrowing.

**Spleen.** Amyloidosis of the spleen often causes moderate or even marked enlargement. For obscure reasons, one of two patterns may develop. The deposits may be virtually limited to the follicles, producing tapioca-like granules on gross examination ("sago spleen"), or they may be principally in the splenic sinuses and eventually extend to the splenic pulp, forming large pale areas ("lardaceous spleen"). In both patterns the spleen is firm in consistency, and cut surface shows waxy deposits.

**Liver.** Amyloidosis of the liver may cause massive enlargement (as much as 9000 g). Grossly, the liver is extremely pale, grayish, and waxy on both the external surface and cut surface. Histologically, **amyloid deposits first appear in the space of Disse** and then progressively encroach on the adjacent hepatic parenchyma and sinusoids (see Fig. 5-37). The sinusoids undergo compression atrophy and are eventually replaced by sheets of amyloid; remarkably, the architecture may be preserved even in the setting of severe involvement.

**Heart.** Amyloidosis of the heart may occur either as isolated organ involvement or as part of a systemic distribution. When accompanied by systemic involvement, it is usually associated with various hematologic dyscrasias. The isolated form (senile amyloidosis) is usually confined to older individuals. Grossly, the heart may not be evident on gross examination, or they may cause minimal to moderate cardiac enlargement. Characteristic gross findings are gray-pink, dewdrop-like subendocardial elevations, particularly in the atrial chambers. On histologic examination, deposits are typically found throughout the myocardium, beginning **between myocardial fibers** and eventually causing their pressure atrophy.

**Other Organs.** Amyloidosis of other organs is generally encountered in systemic forms. The thyroid, and pituitary are common sites of involvement. In this case also the amyloid deposits are in relation to stromal and endothelial cells and progressively encroaches on the parenchyma. Large amounts of amyloid may be present in any of these endocrine glands without causing dysfunction. In the gastrointestinal tract, a relatively favored site, amyloid may be found in the stomach, producing tumorous masses that must be distinguished from neoplasms. Nodular deposits in the tongue may produce **macroglossia**. On the basis of the frequent involvement of the gastrointestinal tract, gingival, intestinal, and rectal biopsies serve in the diagnosis of suspected cases. In the case of microglobulin amyloid in patients receiving long-term dialysis occurs most commonly in the **carpal tunnel syndrome of the wrist**, resulting in compression of the median nerve (carpal tunnel syndrome).

### *Clinical Correlation*

Amyloidosis may be an unsuspected finding at autopsy in a patient who has no apparent related clinical illness. It is responsible for serious clinical dysfunction and even death. All depends on the particular sites of organ involvement. Nonspecific complaints such as weakness, fatigue, and weight loss are the most common.



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## 6 Neoplasia

THOMAS P. STRICKER MD, PhD  
VINAY KUMAR MD

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Cancer is the second leading cause of death in the United States; only cardiovascular diseases exact a higher toll. Even more agonizing than the mortality rate is the emotional and physical suffering inflicted by neoplasms. Patients and the public often ask, "When will there be a cure for cancer?" The answer to this simple question is difficult because cancer is not one disease but many disorders that share a profound growth dysregulation. Some cancers, such as Hodgkin lymphomas, are curable, whereas others, such as cancer of the pancreas, have a high mortality. The only hope for controlling cancer lies in learning more about its pathogenesis, and great strides have been made in understanding the molecular basis of cancer. This chapter deals with the basic biology of neoplasia-the nature of benign and malignant neoplasms and the molecular basis of neoplastic transformation. The host response to tumors and the clinical features of neoplasia are also discussed.



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## NOMENCLATURE

*Neoplasia* literally means "new growth." A neoplasm, as defined by Willis, is "an abnormal mass of cells that is uncoordinated with that of the normal tissues and persists in the same excessive manner after its cessation of growth, invasion, or repair of the change." *Fundamental to the origin of all neoplasms are heritable (genetic) changes that allow the neoplasm to be independent of physiologic growth-regulatory stimuli.* Neoplastic cells are said to be transformed; they are apparently oblivious to the regulatory influences that control normal cell growth. Neoplasms therefore grow more or less steadily increase in size regardless of their local environment and the nutritional environment, but no means complete, however. Some neoplasms require endocrine support, and such dependence is a disadvantage of the neoplasm. All neoplasms depend on the host for their nutrition and blood supply.

In common medical usage, a neoplasm is often referred to as a *tumor*, and the study of tumors is *oncology* (from *oncos*, "tumor" and *logos*, "study of"). In oncology, the division of neoplasms into benign and malignant categories is based on a judgment of a neoplasm's potential clinical behavior.

A tumor is said to be *benign* when its microscopic and gross characteristics are considered to be non-threatening. If it remains localized, it cannot spread to other sites, and is amenable to local surgical removal; the pathologist notes, however, that benign tumors can produce more than localized lumps, and sometimes they are pointed out later.

Malignant tumors are collectively referred to as *cancers*, derived from the Latin word for *crab*—that is, in an obstinate manner, similar to a crab's behavior. *Malignant*, as applied to a neoplasm, implies invasion of adjacent structures and spread to distant sites (metastasize) to cause death. Not all cancers pursue an aggressive course and are treated successfully, but the designation *malignant* constitutes a red flag.

All tumors, benign and malignant, have two basic components: (1) the *parenchyma*, made up of the neoplastic cells, and (2) the *stroma*, supporting, host-derived, non-neoplastic tissue, made up of connective tissue, blood vessels, and lymphatics. The parenchyma of the neoplasm largely determines its biologic behavior, and it is this component from which the tumor is named. The stroma is crucial to the growth of the neoplasm, since it carries the blood supply and provides support. As will be discussed later, stromal cells and neoplastic cells carry on a two-way conversation that

### *Benign Tumors*

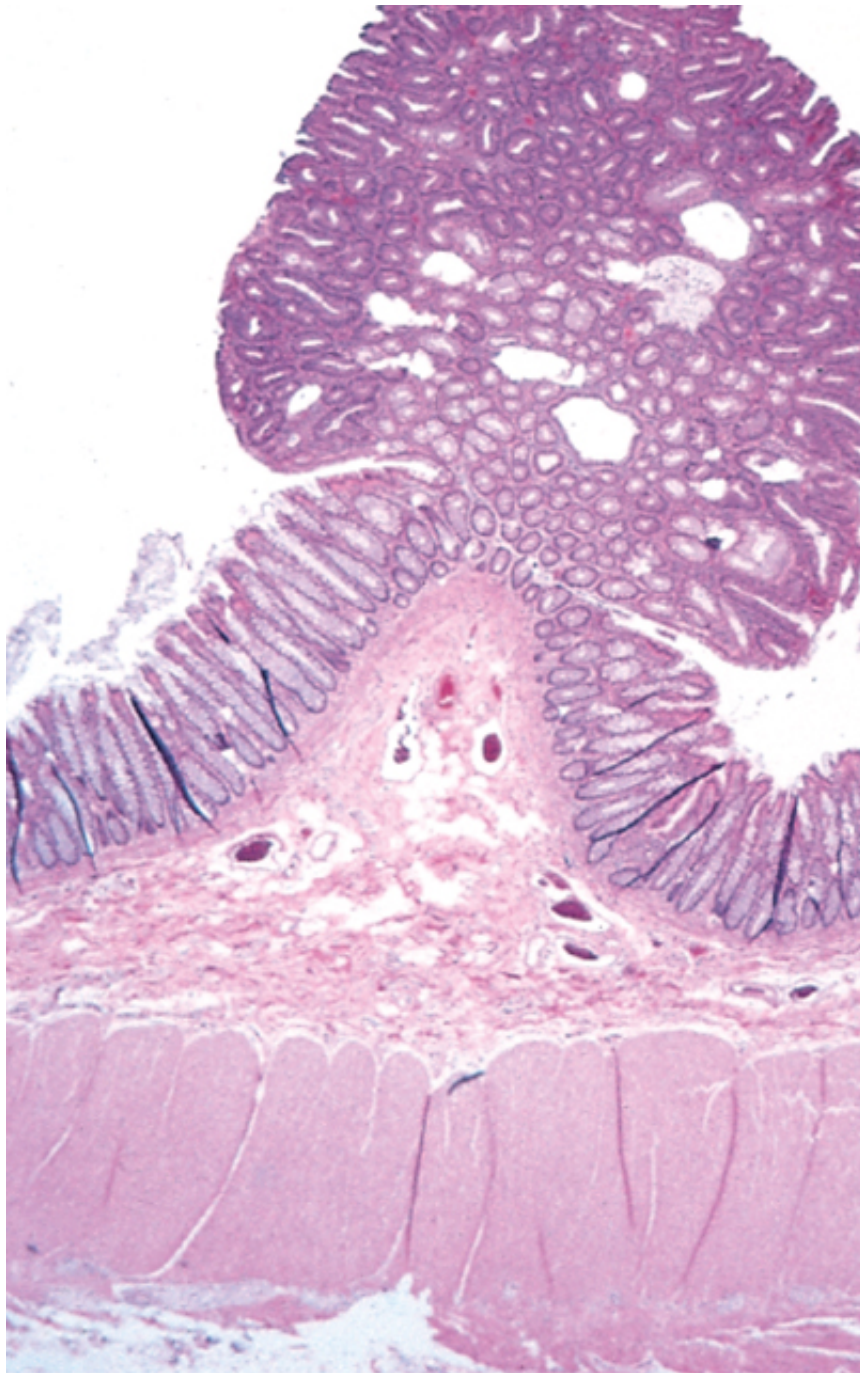
In general, benign tumors are designated by attaching the suffix *-oma* to the cell type from which they arise. A tumor in fibrous tissue is a *fibroma*; a benign cartilaginous tumor is a *chondroma*. The nomenclature of benign tumors is based on the site of origin. They are classified sometimes on the basis of their microscopic pattern and sometimes on the basis of their clinical behavior.

For instance, the term *adenoma* is applied to benign epithelial neoplasms producing glandular patterns, but not necessarily exhibiting glandular patterns. A benign epithelial neoplasm arising from renal tubules would be termed an adenoma, as would a mass of benign epithelial cells that produces no glandular pattern, as in the adrenal cortex. *Papillomas* are benign epithelial neoplasms, growing on any surface, that produce fronds. A *polyp* is a mass that projects above a mucosal surface, as in the gut, to form a macroscopically visible mass. Although this term is commonly used for benign tumors, some malignant tumors also may appear as polyps; typically they are seen in the ovary.

### *Malignant Tumors*

The nomenclature of malignant tumors essentially follows that of benign tumors, with certain additional





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Figure 6-1 Colonic polyp. This benign glandular tumor (adenoma) is projecting into the colonic lumen and is

Malignant neoplasms arising in mesenchymal tissue or its derivatives are called *sarcomas*. A cancer arising in connective tissue is a *fibrosarcoma*, and a malignant neoplasm composed of chondrocytes is a *chondrosarcoma*. Sarcomas are named according to the cell type of which they are composed. Malignant neoplasms of epithelial cell origin are called *carcinomas*. The fact that the epithelia of the body are derived from all three germ-cell layers; a malignant neoplasm arising in the connective tissue (mesoderm) is a carcinoma, as are the cancers arising in the skin (ectoderm) and lining epithelium (endoderm). Malignant neoplasms arising in the mesoderm may give rise to carcinomas (epithelial) and sarcomas (mesenchymal). Carcinomas may grow in a glandular pattern are called *adenocarcinomas*, and those that produce squamous cells are called *squamous carcinomas*. Sometimes the tissue or organ of origin can be identified, as in the designation of renal cell adenocarcinoma, which implies an origin from bile ducts. Sometimes the tumor shows little or no differentiation and must be



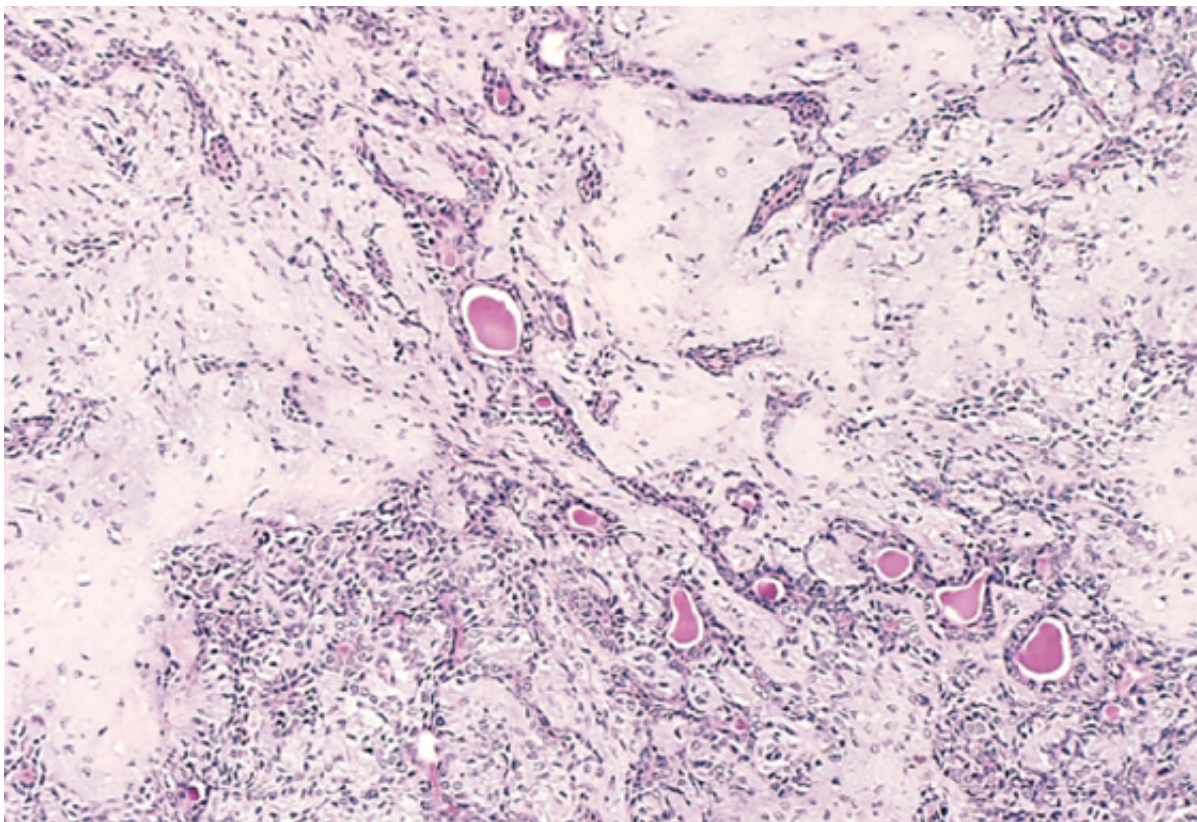
*undifferentiated carcinoma*.

The parenchymal cells in a neoplasm, whether benign or malignant, resemble each other, as though from a single progenitor. Indeed, neoplasms are of monoclonal origin, as is discussed later. In some instances, *divergent differentiation*, creating so-called *mixed tumors*. The best example is mixed tumor of salivary gland, where epithelial components are dispersed throughout a fibromyxoid stroma, sometimes harboring islands of diverse elements are thought to derive from epithelial cells, myoepithelial cells, or both in the salivary gland. One of these neoplasms is *pleomorphic adenoma*. Fibroadenoma of the female breast is another common example. If the fibrous component is neoplastic, the term *fibroadenoma* remains in common usage.

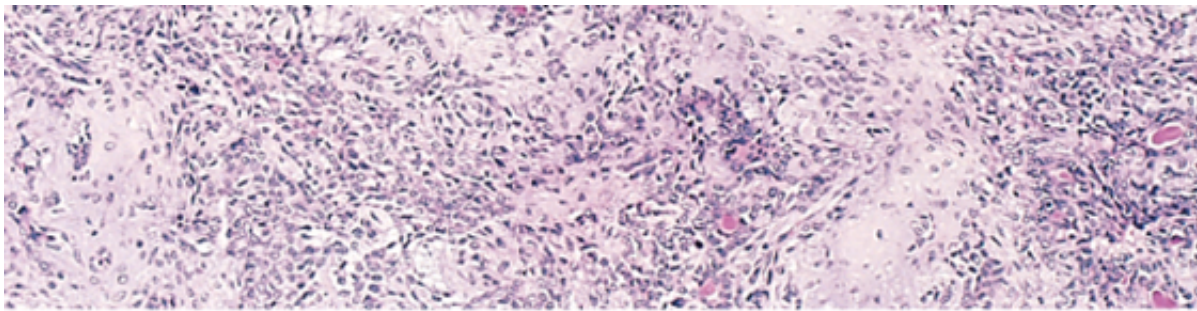
The multifaceted mixed tumors should not be confused with a *teratoma*, which contains recognizable elements representative of more than one germ-cell layer and sometimes all three. Teratomas originate from cells that are normally present in the ovary and testis and sometimes abnormally present in sequestered midline locations. They have the capacity to differentiate into any of the cell types found in the adult body and so, not surprisingly, in a helter-skelter fashion, bits of bone, epithelium, muscle, fat, nerve, and other tissues.

The specific names of the more common forms of neoplasms are presented in [Table 6-1](#). Some of the more common, for example, the terms *lymphoma*, *mesothelioma*, *melanoma*, and *seminoma* are used for malignant neoplasms and are firmly entrenched in medical terminology.

There are other instances of confusing terminology. *Hamartoma* is a malformation that presents as a mass indigenous to the particular site. One may see a mass of mature but disorganized hepatic cells, blood vessels, and bile ducts within the liver, or there may be a hamartomatous nodule in the lung containing islands of cartilage. A more appropriate misnomer is the term *choristoma*. This congenital anomaly is better described as a *heterotopic rest*. A well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach. This heterotopic rest may be replete with islets of Langerhans and exocrine glands. The term *choristoma* is used for the heterotopic rest a gravity far beyond its usual trivial significance. Although the terminology of rests is not as important because it is the language by which the nature and significance of tumors are categorized.







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Figure 6-2 Mixed tumor of the parotid gland contains epithelial cells forming ducts and myxoid stroma that resen  
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Table 6-1. Nomenclature of Tumors

Tissue of Origin	Benign
<b>Composed of One Parenchymal Cell Type</b>	
Connective tissue and derivatives	Fibroma
	Lipoma
	Chondroma
	Osteoma
<b>Endothelial and related tissues</b>	
Blood vessels	Hemangioma
Lymph vessels	Lymphangioma
Synovium	
Mesothelium	
Brain coverings	Meningioma
<b>Blood cells and related cells</b>	
Hematopoietic cells	
Lymphoid tissue	
<b>Muscle</b>	
Smooth	Leiomyoma
Striated	Rhabdomyoma
<b>Tumors of epithelial origin</b>	
Stratified squamous	Squamous cell papilloma
Basal cells of skin or adnexa	
Epithelial lining of glands or ducts	Adenoma
	Papilloma
	Cystadenoma
Respiratory passages	Bronchial adenoma
Renal epithelium	Renal tubular adenoma
Liver cells	Liver cell adenoma
Urinary tract epithelium (transitional)	Urothelial papilloma
Placental epithelium	Hydatidiform mole
Testicular epithelium (germ cells)	
<b>Tumors of melanocytes</b>	Nevus
<b>More Than One Neoplastic Cell Type-Mixed Tumors, Usually Derived from One Germ Cell Layer</b>	

Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)
Renal anlage	
<b>More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer-Teratogenous</b>	
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst



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## CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

Nothing is more important to the patient with a tumor than being told "It is benign." In most instances, the remarkable accuracy based on long-established clinical and anatomic criteria, but some neoplasms may indicate innocence, and others may indicate malignancy. These problems are not the fundamental features by which benign and malignant tumors can be distinguished. These are difficult local invasion, and metastasis.

### Differentiation and Anaplasia

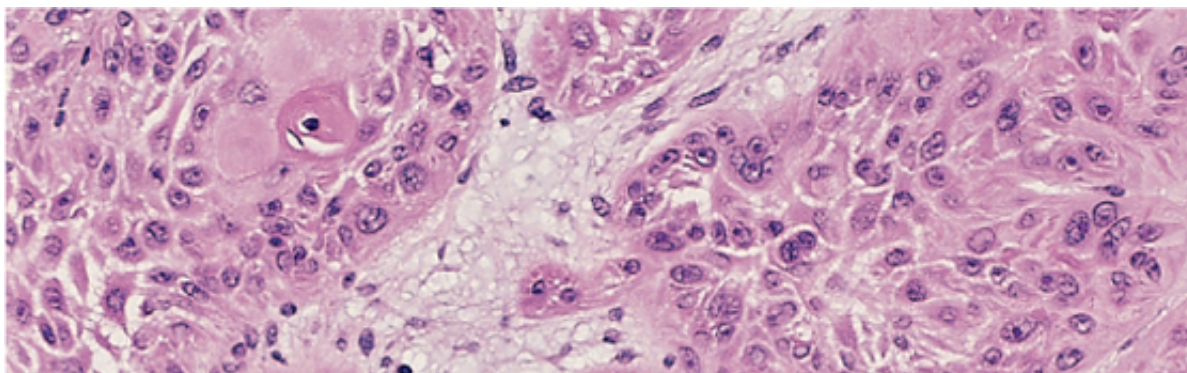
Differentiation and anaplasia refer only to the parenchymal cells that constitute the transformed cell. The extent to which they resemble their normal forebears morphologically. Carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant. The consistency of a neoplasm. Certain carcinoma (desmoplasia), making them hard, so-called scirrhous tumors.

Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts. For example, a lipoma is made up of mature fat cells laden with cytoplasmic lipid vacuoles, and a chondroma is made up of mature cartilage cells in a cartilaginous matrix-evidence of morphologic and functional differentiation. In well-differentiated benign tumors, the cells are scant in number and are of normal configuration.

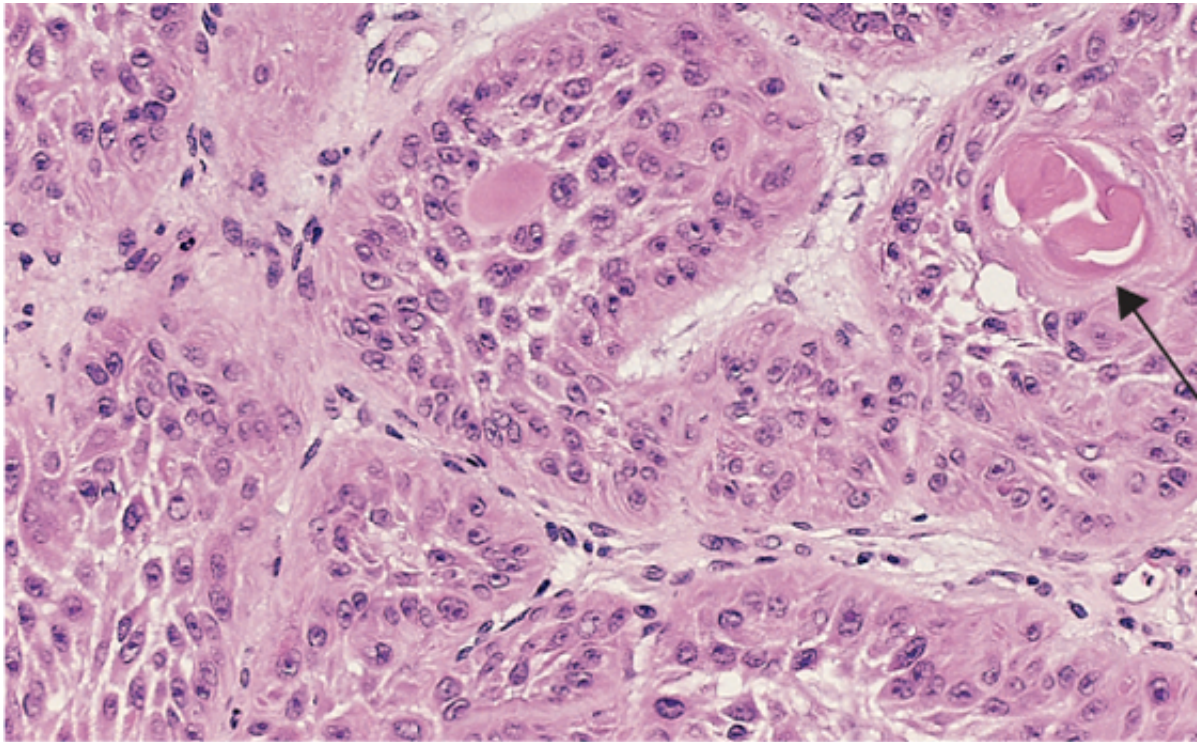
Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation, from completely undifferentiated. For example, well-differentiated adenocarcinomas of the thyroid may sometimes be difficult to distinguish from benign proliferations. Between the two extremes are *moderately well differentiated*.

The better the differentiation of the cell, the more completely it retains the functional capabilities of the normal cell. Some neoplasms and even well-differentiated cancers of endocrine glands frequently elaborate the hormone of the normal gland. For example, well-differentiated squamous cell carcinomas elaborate keratin (see [Fig. 6-3](#)), just as well-differentiated endocrine glands elaborate hormone. In other instances unanticipated functions emerge. Some cancers may elaborate fetal proteins. Some cancers may elaborate fetal protein in the adult. Cancers of nonendocrine origin may produce so-called ectopic hormones. For example, an adenocarcinoma may produce adrenocorticotrophic hormone (ACTH), parathyroid-like hormone, insulin, glucagon, and others. Most of the time, *the more rapidly growing and the more anaplastic a tumor, the less likely it is*

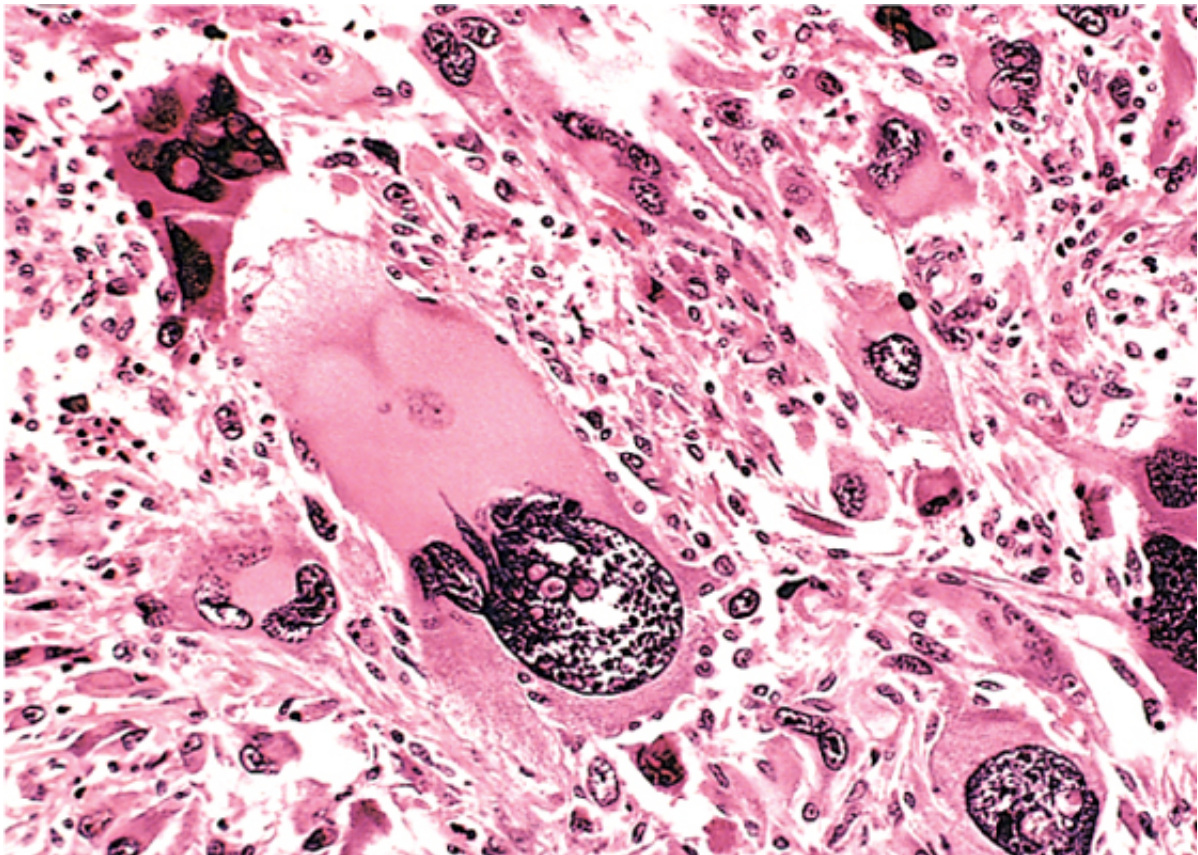
Malignant neoplasms that are composed of undifferentiated cells are said to be *anaplastic*. Lack of differentiation is considered a hallmark of malignancy. The term *anaplasia* literally means "to form backward." It implies a loss of structural and functional differentiation of normal cells. It is now known, however, that at least some tumors are composed of dedifferentiated cells; in these tumors failure of differentiation, rather than dedifferentiation of specialized cells, is the primary event. Recent studies also indicate that, in some cases dedifferentiation of apparently mature cells does



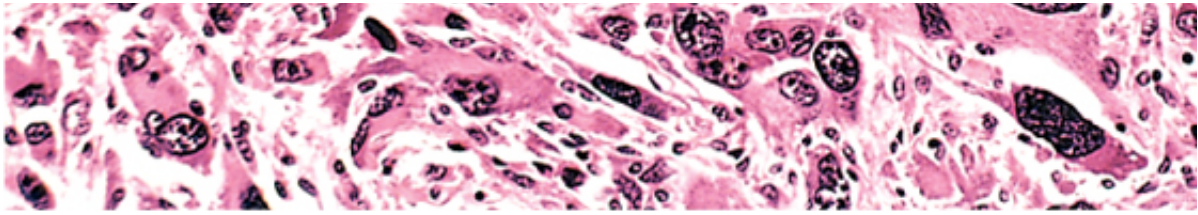




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 Figure 6-3 Well-differentiated squamous cell carcinoma of the skin. The tumor cells are strikingly similar to normal keratinocytes, with abundant keratinization, intercellular bridges, and nests of keratin pearls (arrow). (Courtesy of Dr. Trace Worrell, Department of Pathology University of Texas.)

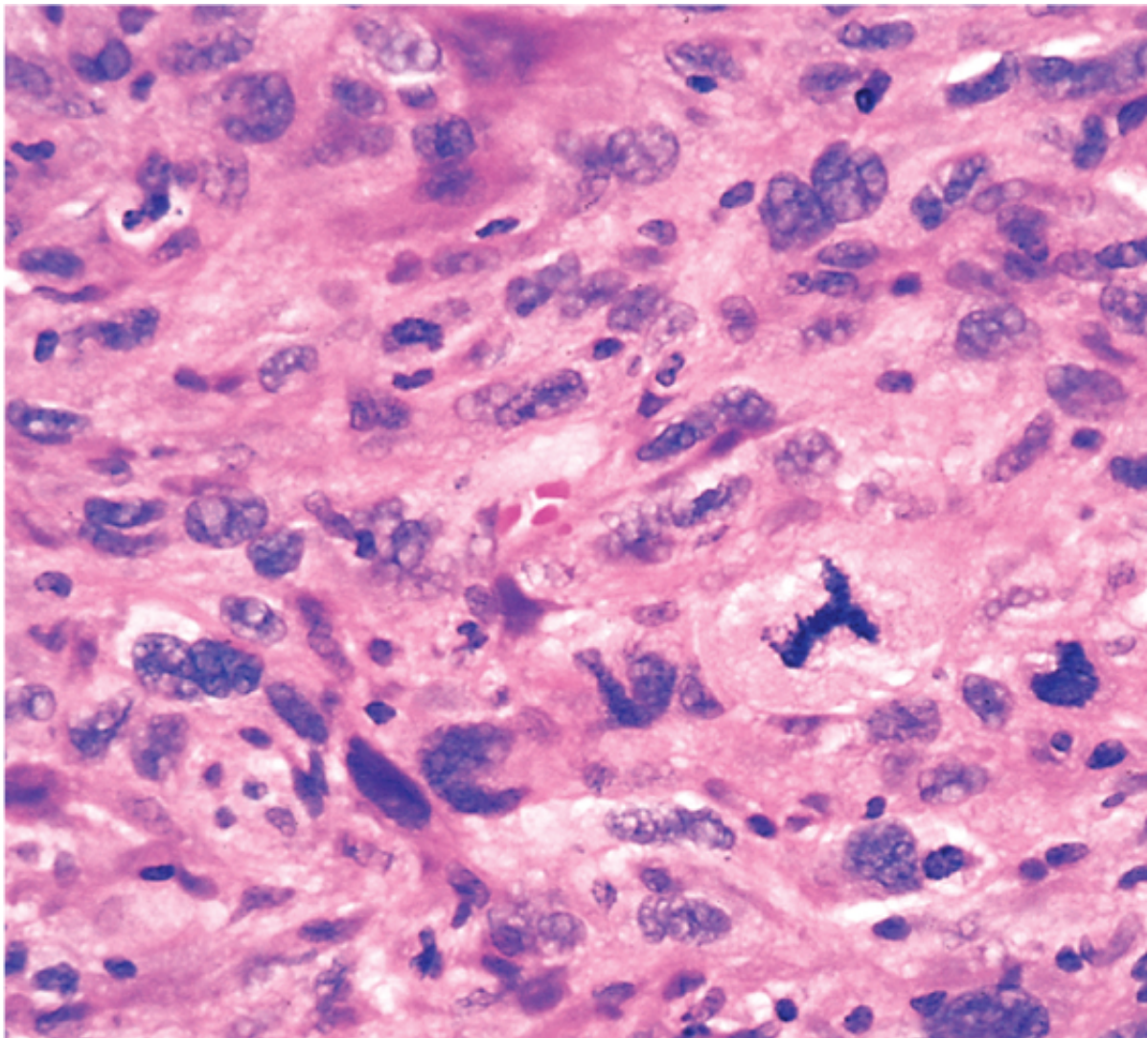






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 Figure 6-4 Anaplastic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, including giant cells. (Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical Center)

Anaplastic cells display marked *pleomorphism* (i.e., marked variation in size and shape) (Fig. 6-4) and are *extremely hyperchromatic* (darkly stained) and large. The nuclear-to-cytoplasmic ratio may approach 1:1. *Giant cells* that are considerably larger than their neighbors may be formed and possess either multiple nuclei or a single large nucleus. *Anaplastic nuclei are variable and bizarre in size and shape.* The chromatin is coarse and clumped. More important, *mitoses are often numerous and distinctly atypical*; anaplastic mitoses may be multipolar, tripolar or quadripolar forms (Fig. 6-5). Also, anaplastic cells usually fail to develop recognizable polarity (they lose normal polarity). They may grow in sheets, with total loss of communal structures, such as squamous architecture. Anaplasia is the most extreme disturbance in cell growth encountered in tumors.

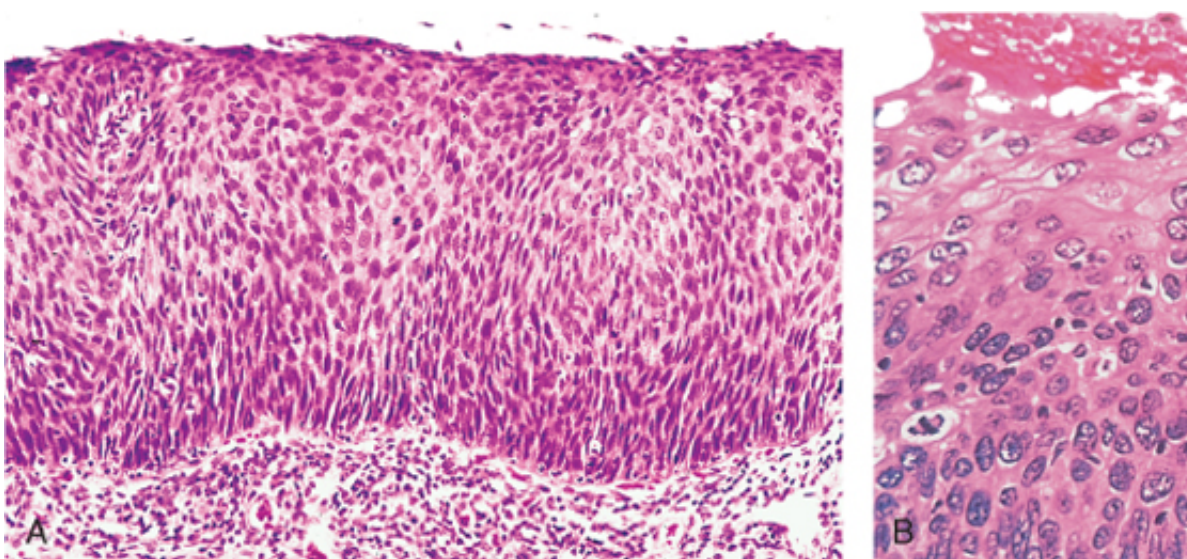




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Figure 6-5 High-power detail view of anaplastic tumor cells shows cellular and nuclear variation in size and shape, including an abnormal tripolar spindle.

Before we leave the subject of differentiation and anaplasia, we should discuss *dysplasia*, a term for neoplastic proliferation. Dysplasia is encountered principally in the epithelia. It is a *loss in the uniform architectural orientation*. Dysplastic cells exhibit considerable pleomorphism and often possess nuclei large for the size of the cell. Mitotic figures are more abundant than usual. Frequently the mitoses appear at all levels and even in surface cells. There is considerable architectural anarchy. For example, tall cells in the basal layer to flattened squames on the surface may be lost and replaced by dysplastic appearing cells (Fig. 6-6). When dysplastic changes are marked and involve the entire thickness of the epithelium, as *carcinoma in situ*, a pre-invasive stage of cancer (Chapter 19). Although dysplastic changes are a step toward malignant transformation, and long-term studies of cigarette smokers show that epithelial dysplasia is a precursor appearance of cancer, *the term dysplasia without qualifications does not indicate cancer, and dysplasia is not cancer*. Mild-to-moderate changes that do not involve the entire thickness of epithelium may be reversible. In the absence of inciting causes, the epithelium may revert to normal.

### Rate of Growth



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Figure 6-6 A, Carcinoma in situ. Low-power view shows the entire thickness of the epithelium is replaced by dysplastic cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma. Panel B shows a higher magnification view of the dysplastic cells, highlighting nuclear and cellular pleomorphism, and numerous mitotic figures extending to the basement membrane (below) is not seen in this section.

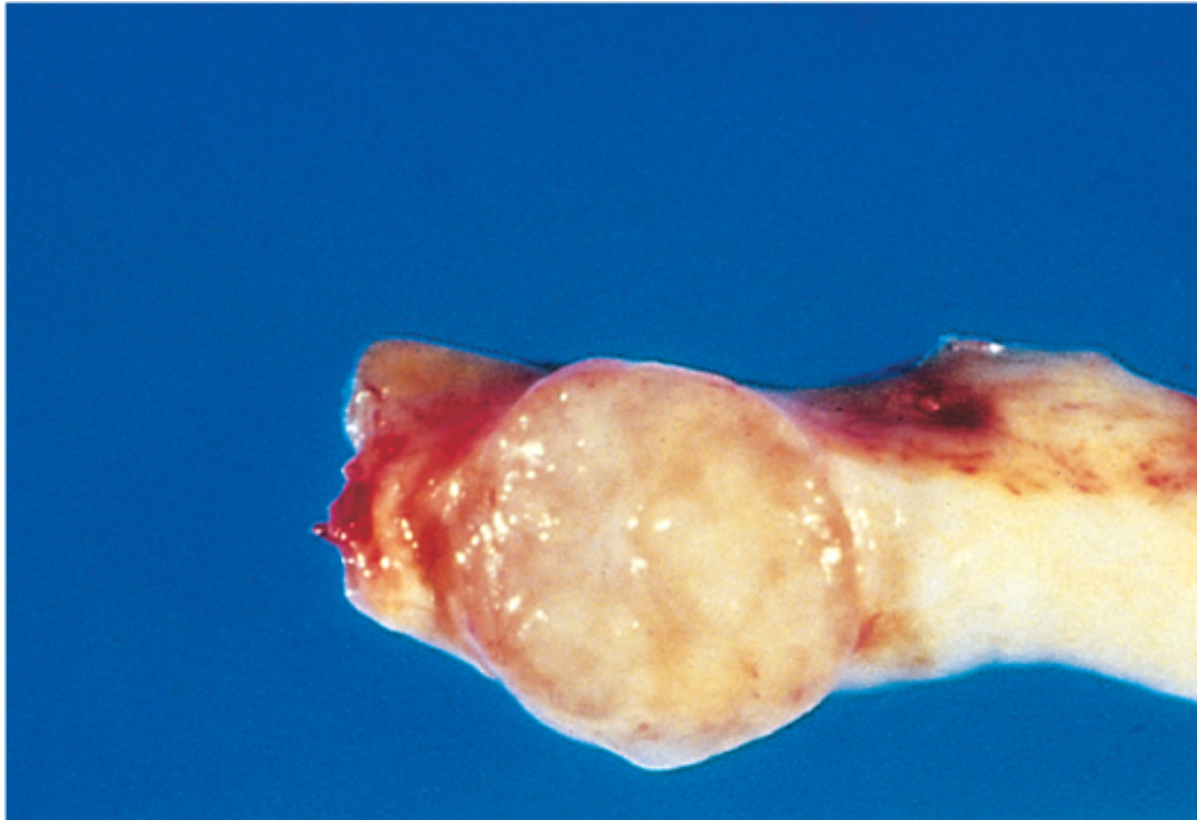
Most benign tumors grow slowly, and most cancers grow much faster, eventually spreading locally and causing death. There are many exceptions to this generalization, however, and some benign tumors grow rapidly. For example, the rate of growth of leiomyomas (benign smooth muscle tumors) of the uterus is influenced by estrogens. They may increase rapidly in size during pregnancy then cease growing, becoming large again after menopause. Influences, such as adequacy of blood supply or pressure constraints, also may affect the growth of tumors. Pituitary gland locked into the sella turcica have been observed to shrink suddenly. Presumably, the progressive enlargement compresses their blood supply. Despite these caveats and the variation in growth rates, it is generally true that most benign tumors increase in size slowly over the span of months to years.

*The rate of growth of malignant tumors correlates in general with their level of differentiation.* In other words, the more poorly differentiated the tumor, the faster it grows. However, there is wide variation in the rate of growth. Some grow slowly, and some grow rapidly.



... poorly understood phenomenon, there is also variation in the rate of growth. Some grow slowly, signifying the emergence of an aggressive subclone of transformed cells. Others grow relatively slowly, and in exceptional instances when growth comes almost to a standstill. Even more exceptionally, some have disappeared spontaneously as they have become totally necrotic, leaving only secondary metastases. In most cancers progressively enlarge over time, some slowly, others rapidly, but the notion that they are benign is not always true. Many lines of experimental and clinical evidence document that most if not all cancers take years to become clinically overt lesions. Rapidly growing malignant tumors often contain central areas of ischemic necrosis. The host, derived from the host, fails to keep pace with the oxygen needs of the expanding mass of cells.

### *Cancer Stem Cells and Lineages*



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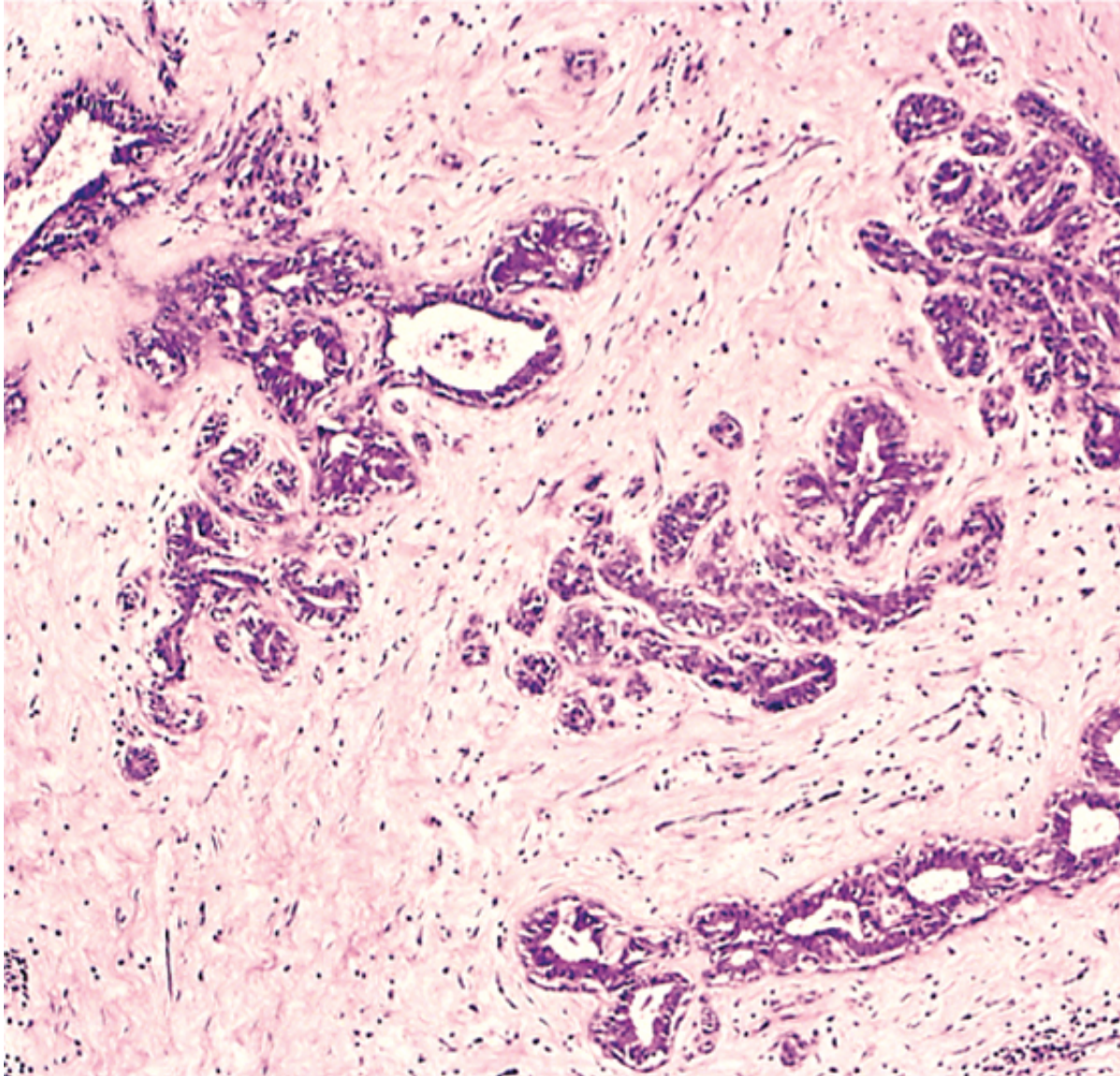
Figure 6-7 Fibroadenoma of the breast. The tan-colored, encapsulated small tumor is sharply demarcated from the surrounding tissue.

A clinically detectable tumor contains a heterogeneous population of cells, which originated from the same cell. It has been hypothesized that this population contains cancer stem cells, which, in analogy to tissue stem cells, sustain the tumor. Recently, cancer stem cells, sometimes called tumor-initiating cells, were identified in several types of tumors, including glioblastoma multiforme (a brain tumor), and acute myeloid leukemia. Cancer stem cells constitute fewer than 2% to 1.0% of cells in acute myeloid leukemia. These findings have important implications for cancer therapy. If the progeny of cancer stem cells would leave in place the cells capable of regenerating the tumor, then the tumor is not yet clear.

### **Local Invasion**

A benign neoplasm remains localized at its site of origin. It does not have the capacity to infiltrate, as do malignant neoplasms. For example, as fibromas and adenomas slowly expand, most develop a capsule that separates them from the host tissue. This capsule probably is derived from the stroma of the host tissue under the pressure of the expanding tumor. The stroma of the tumor itself also may contribute to the capsule. It should be emphasized, however, that *not all benign neoplasms are encapsulated*. For example, the leiomyoma is demarcated from the surrounding smooth muscle by a zone of compressed and attenuated normal tissue.

demarcated from the surrounding smooth muscle by a zone of compressed and attenuated normal developed capsule. Nonetheless, a well-defined cleavage plane exists around these lesions. A few are not discretely defined; this is particularly true of some vascular benign neoplasms of the dermis. This emphasizes that although encapsulation is the rule in benign tumors, the lack of a capsule does not



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Figure 6-8 Microscopic view of fibroadenoma of the breast seen in Figure 6-7. The fibrous capsule (right) sharply  
(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Me

*Cancers grow by progressive infiltration, invasion, destruction, and penetration of the surrounding* develop well-defined capsules. There are, however, occasional instances in which a slowly growing tumor to be encased by the stroma of the surrounding host tissue, but microscopic examination usually reveals a sharp margin and infiltrating adjacent structures. The infiltrative mode of growth makes it necessary to re-examine normal tissue when surgical excision of a malignant tumor is attempted. Surgical pathologists carefully examine tumors to ensure that they are devoid of cancer cells (*clean margins*). *Next to the development of* most reliable feature that distinguishes malignant from benign tumors.

### Metastasis

The term *metastasis* connotes the development of secondary implants (metastases) discontinuous



tissues (Fig. 6-11). *The properties of invasiveness and, even more so, metastasis, more unequivocal than any of the other attributes of a tumor.* Not all cancers have equivalent ability to metastasize, but carcinomas of the skin and most primary tumors of the central nervous system that are highly invasive rarely metastasize. At the other extreme are osteogenic (bone) sarcomas, which usually have metastases at the time of discovery.

Approximately 30% of newly diagnosed patients with solid tumors (excluding skin cancers other than melanoma) have evident metastases. An additional 20% have occult (hidden) metastases at the time of diagnosis.



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Figure 6-9 Cut section of invasive ductal carcinoma of the breast. The lesion is retracted, infiltrating the surrounding tissue, and is palpable.

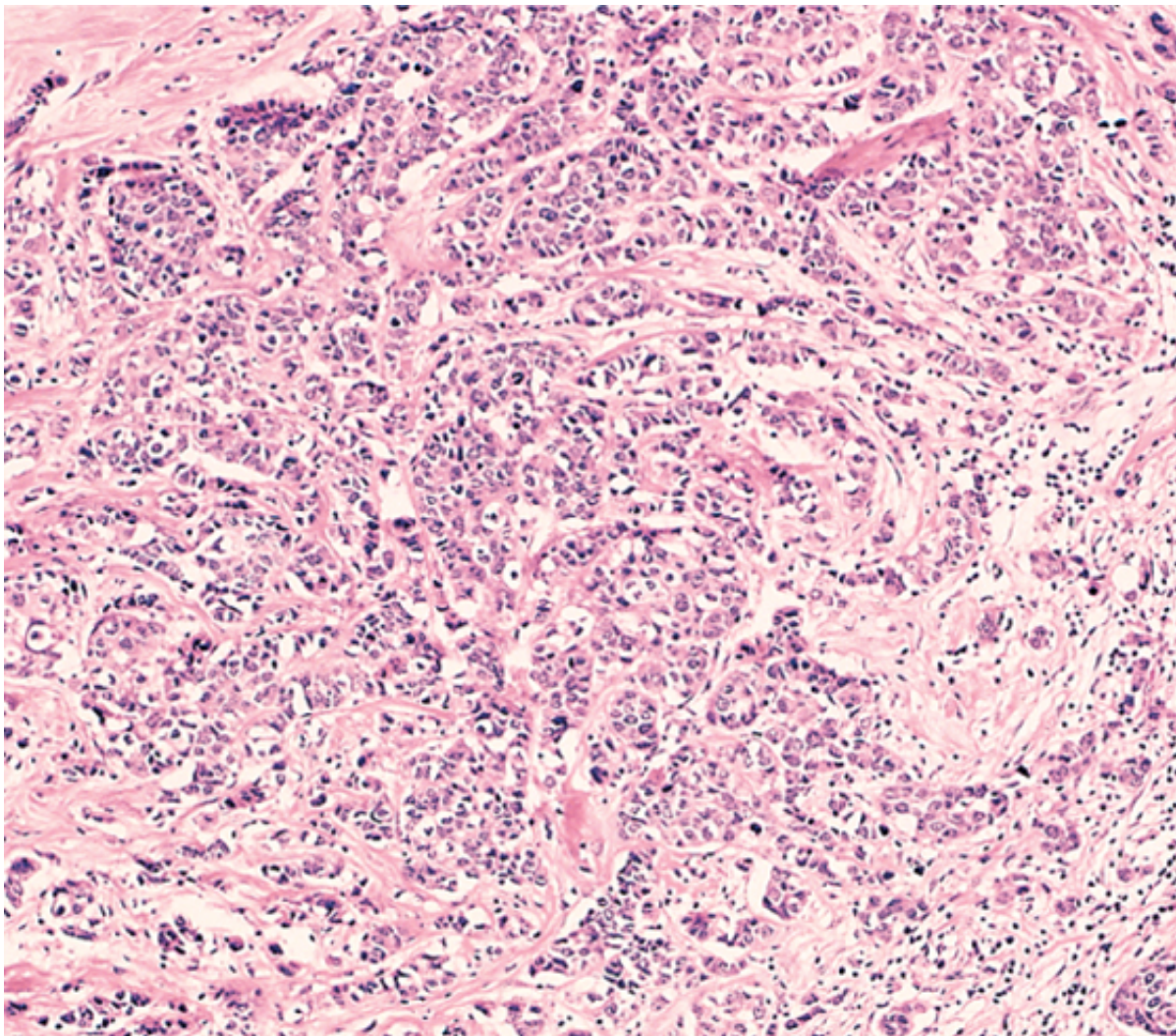
In general, the more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread. Extremely small cancers have been known to metastasize, and, conversely, some large and ominous primary tumors do not metastasize. Dissemination strongly prejudices, if it does not exclude, the possibility of cure of the disease, as

Dissemination strongly prejudices, if it does not preclude, the possibility of cure of the disease, so cancer, no achievement would confer greater benefit on patients than methods to prevent metastasis.

Malignant neoplasms disseminate by one of three pathways: (1) seeding within body cavities, (2) lymphatic spread, and (3) hematogenous spread.

*Spread by seeding* occurs when neoplasms invade a natural body cavity. This mode of dissemination is characteristic of cancers of the ovary, which often cover the peritoneal surfaces widely. The implants literally may invade the underlying parenchyma of the abdominal organs. Here is an instance of the ability to reseed, which is separable from the capacity to invade. Neoplasms of the central nervous system, such as a medulloblastoma, may penetrate the cerebral ventricles and be carried by the cerebrospinal fluid to reimplant on the meninges or in the spinal cord.

*Lymphatic spread* is more typical of carcinomas, whereas *hematogenous spread* is favored by sarcomas. There are close interconnections, however, between the lymphatic and vascular systems, and so all forms of cancer may spread through both systems. The pattern of lymph node involvement depends principally on the site of the primary tumor and the lymphatic drainage of the site. Lung carcinomas arising in the respiratory passages metastasize first to the tracheobronchial and hilar nodes. Carcinoma of the breast usually arises in the upper outer quadrant and drains to the axillary nodes. However, medial breast lesions may drain through the chest wall to the nodes along the internal mammary vessels. Thereafter, in both instances, the supraclavicular and infraclavicular nodes may be seeded. In sarcomas, the tumor cells may traverse the lymphatic channels within the immediately proximate nodes to be trapped in subsequent nodes, a process called *skip metastases*. The cells may traverse all of the lymph nodes ultimately to reach the vascular circulation.



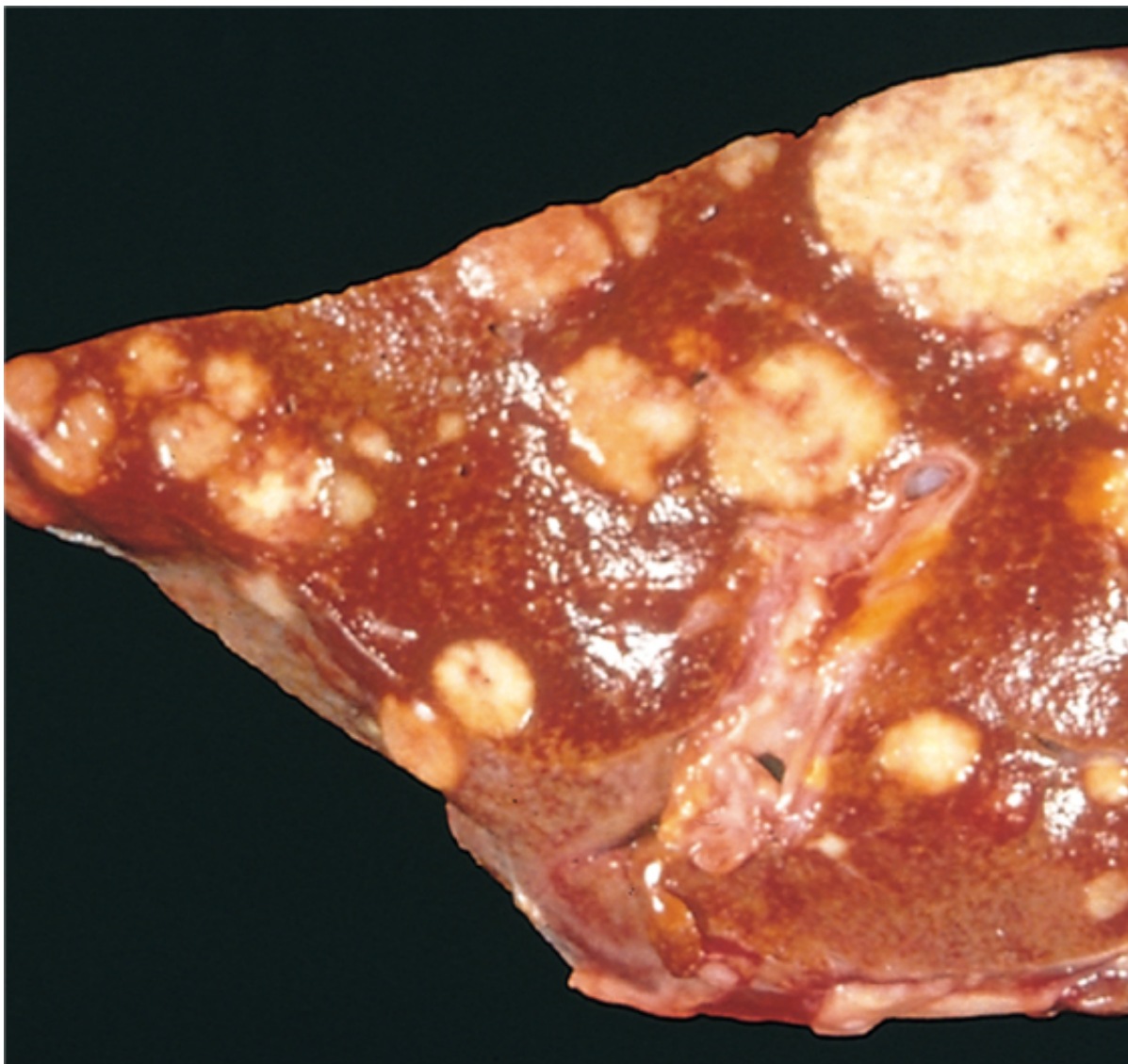




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Figure 6-10 Microscopic view of breast carcinoma seen in Figure 6-9 illustrates the invasion of breast stroma and with Fig. 6-8). Note the absence of a well-defined capsule. (Courtesy of Dr. Trace Worrell, Department of Pathology School, Dallas, Texas.)

A "sentinel lymph node" is defined as the first lymph node in a regional lymphatic basin that receives lymph from the primary site. It can be delineated by injection of blue dyes or radiolabelled tracers. Biopsy of sentinel lymph node can detect spread of tumor, and can be used to plan treatment.

It should be noted that although enlargement of nodes near a primary neoplasm should arouse suspicion, it does not always imply cancerous involvement. The necrotic products of the neoplasm and tumor cells can enter the nodes, such as enlargement and hyperplasia of the follicles (lymphadenitis) and proliferation of sinusoids (sinus histiocytosis).



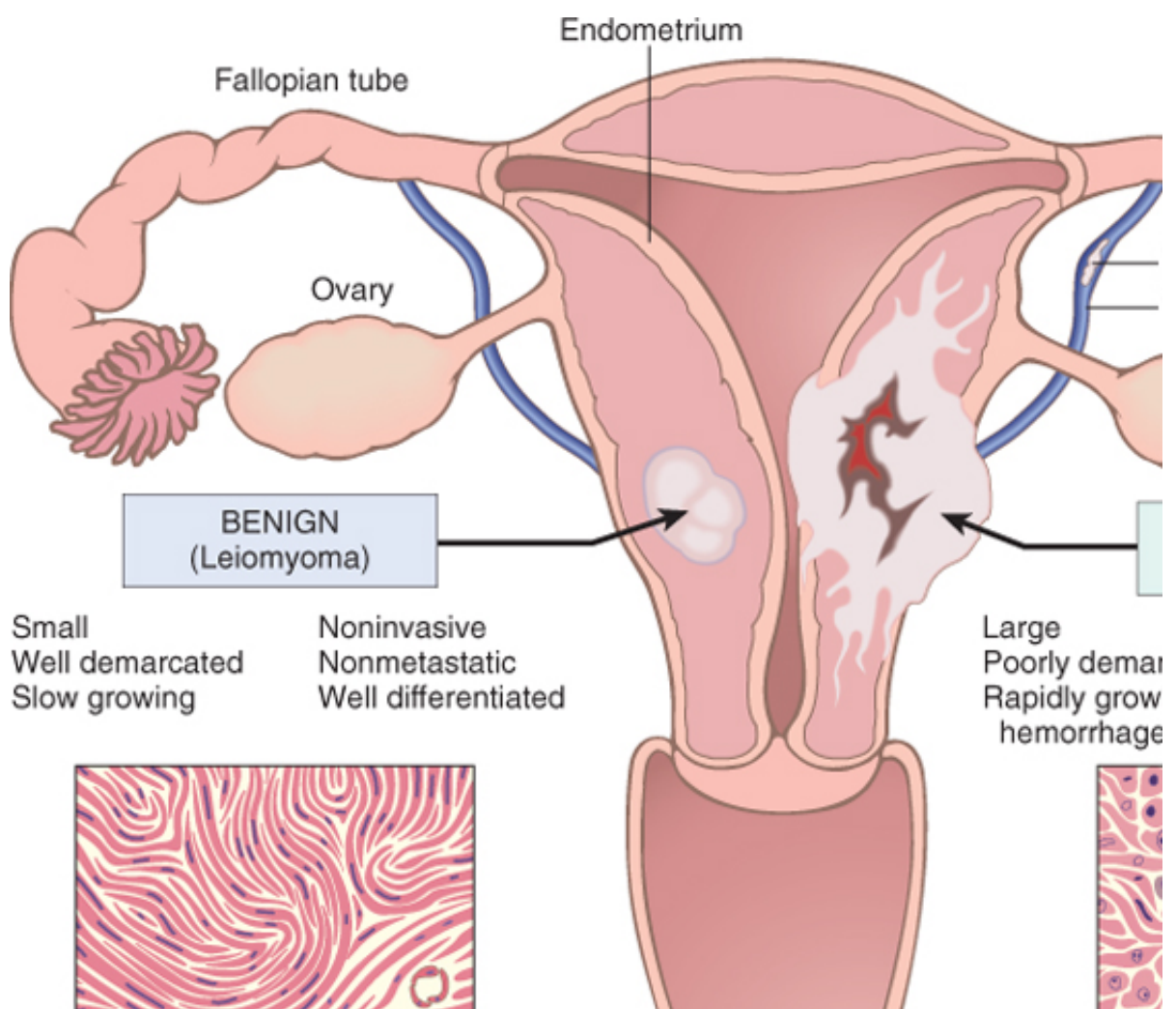
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Figure 6-11 A liver studded with metastatic cancer.

*Hematogenous spread* is the most feared consequence of a cancer. It is the favored pathway for : As might be expected, arteries are penetrated less readily than are veins. With venous invasion, t flow draining the site of the neoplasm, with tumor cells often stopping in the first capillary bed they flows to the liver, and all caval blood flows to the lungs, *the liver and lungs are the most frequently hematogenous dissemination*. Cancers arising near the vertebral column often embolize through t probably is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate

Certain carcinomas have a propensity to invade veins. Renal cell carcinoma often invades the rer the inferior vena cava, sometimes reaching the right side of the heart. Hepatocellular carcinomas radicles to grow within them into the main venous channels. Remarkably, such intravenous growth widespread dissemination.

Many observations suggest that mere anatomic localization of the neoplasm and natural pathway: explain the systemic distributions of metastases. For example, prostatic carcinoma preferentially s carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver an although rich in capillaries, are rarely the site of secondary deposits. The molecular basis of such discussed later.

In conclusion, the various features discussed in the preceding sections, as summarized below and differentiation of benign and malignant neoplasms. Against this background of the structure and b some considerations of their nature and origins.







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Figure 6-12 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor (leiomyosarcoma).

## SUMMARY

### Characteristics of Benign and Malignant Tumors

Benign and malignant tumors can be distinguished on the basis of the degree of growth, local invasiveness, and distant spread. Benign tumors resemble the well differentiated; malignant tumors are poorly or completely undifferentiated. Benign tumors are slow growing, whereas malignant tumors generally grow faster. Benign tumors are circumscribed and have a capsule; malignant tumors are poorly circumscribed and surround normal tissues. Benign tumors remain localized to the site of origin; malignant tumors are locally invasive and they metastasize to distant sites.



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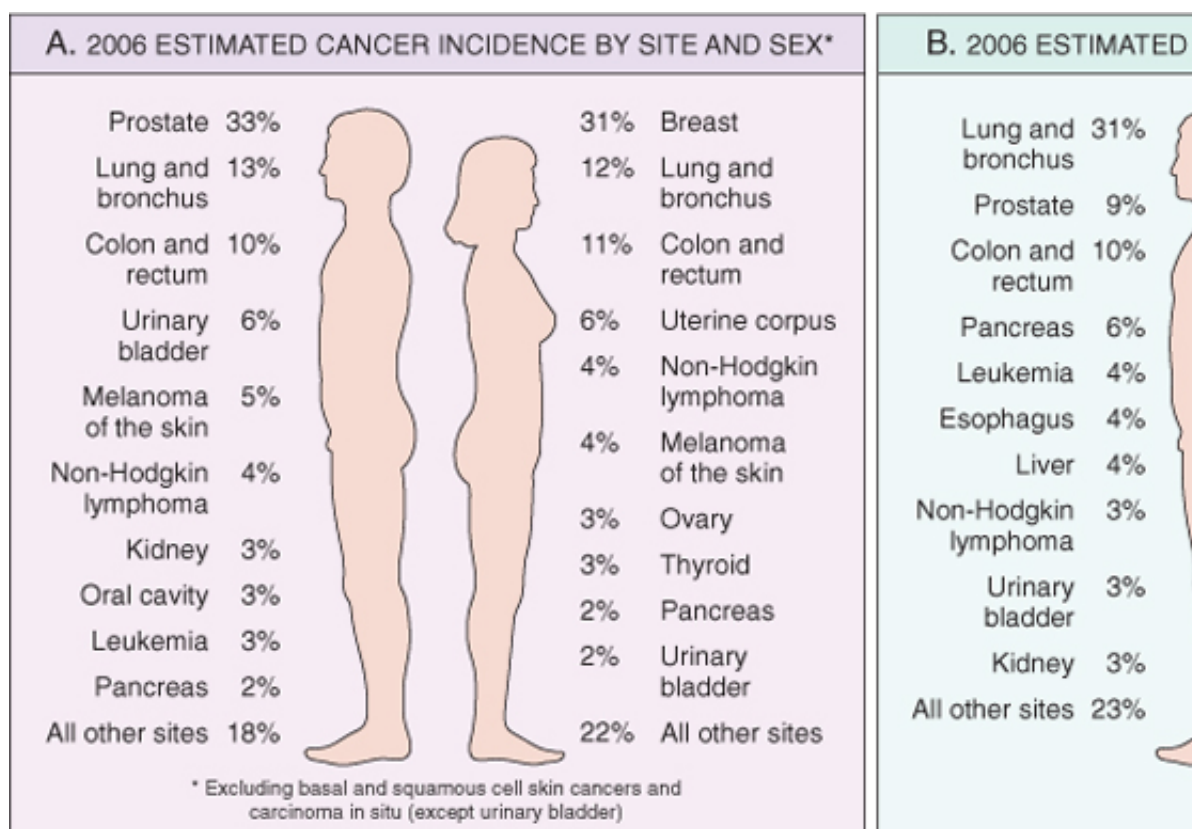
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## EPIDEMIOLOGY

Because cancer is a disorder of cell growth and behavior, its ultimate cause must be defined at the cellular level. However, epidemiology can contribute substantially to knowledge about the origin of cancer. The now well-established link between smoking and lung cancer arose primarily from epidemiologic studies. A correlation between dietary patterns in the western world and Africa led to the recognition that dietary fat and fiber intake influenced the causation of this cancer. Major insights into the causes of cancer can be obtained by epidemiologic studies. Environmental, racial (possibly hereditary), and cultural influences to the occurrence of specific neoplasms. Factors with an increased risk of developing cancer (preneoplastic disorders) also provide clues to the pathogenesis of cancer. In this discussion we first summarize the overall incidence of cancer to gain an insight into the magnitude of the problem. Some issues relating to the patient and environment that influence the predisposition to cancer.

### Cancer Incidence

Some perspective on the likelihood of developing a specific form of cancer can be gained from national cancer statistics. Overall, it is estimated that about 1.4 million new cancer cases will occur in 2006, and 565,000 people will die from cancer in the United States. The incidence of the most common forms of cancer and the major killers is presented in Figure 6-13.



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Figure 6-13 Cancer incidence and mortality by site and sex. (Adapted from Jemal A, et al.: Cancer statistics, 2006. CA Cancer J Clin 2006; 56:5-26.)

Over several decades, the death rates of many forms of malignant neoplasia have changed. Part of the decline in the overall cancer death rate among men that was attributable largely to lung cancer, but this has been offset by an increase in the death rate from prostate cancer. The overall death rate among women has fallen slightly, mostly as a result of the decline in death rates from stomach, colon, and large bowel. These welcome trends have more than counterbalanced the striking increase in the death rate from breast cancer.

stomach, and large bowel. These welcome trends have more than counterbalanced the striking of women, which not long ago was a relatively uncommon form of neoplasia in this sex. The decline is directly related to widespread use of cytologic smear studies for early detection of this tumor while in death rates for cancers of the stomach are obscure; however, there have been speculations about carcinogens.

### Geographic and Environmental Variables

Although many impressive advances in understanding the molecular pathogenesis of cancer have been made, it is fair to state that environmental factors that give rise to somatic mutations are the prime cause of sporadic cancers. This notion is supported by the geographic differences in death rates from specific cancers. Rates from breast cancer are about fourfold to fivefold higher in the United States and Europe compared with Japan. The rate for stomach carcinoma in men and women is about seven times higher in Japan than in the United States but is the most lethal cancer among many African populations. These geographic differences are environmental rather than genetic in origin. Nisei (second-generation Japanese in the United States) have mortality rates for certain forms of cancer that are intermediate between those of native-born Americans and those who have lived in the United States for many generations. The two rates come closer with each passing generation.

**Table 6-2. Occupational Cancers**

Agents or Groups of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting. Component of alloys, electrical equipment, medications and herbicides, fungicides, and animal drugs
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire resistance. Found in existing construction as well as fire-resistant textiles, floor underlayment and roofing papers, and floor tiles
Benzene	Leukemia, Hodgkin lymphoma	Principal component of light oil. Although use as solvent has declined, it exists in printing and lithography, paint, rubber, dry cleaning, and detergents. Formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung	Missile fuel and space vehicles. Hardener for lightweight alloys for aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors. Found in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Ethylene oxide	Leukemia	Ripening agent for fruits and nuts. Used in rocket propellant, fumigants for foodstuffs and textiles, and in sterilants for medical equipment
Nickel compounds	Nose, lung	Nickel plating. Component of ferrous alloys, ceramics, and steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium. Can be a significant source of exposure in homes with radon gas
Vinyl chloride	Angiosarcoma, liver	Refrigerant. Monomer for vinyl polymers. Adhesive for plastic containers

Modified from Stellman JM, Stellman SD: Cancer and workplace. *CA Cancer J Clin* 46:70-92, 1996 with permission from Lippincott Williams & Wilkins

There is no paucity of environmental carcinogens. They lurk in the ambient environment, in the workplace, and in our daily lives. They can be as universal as sunlight, can be found particularly in urban settings (e.g., air pollution), and can be found in our occupation (Table 6-2). Certain features of diet have been implicated as possible predisposing influences, the most distressing are those incurred in personal practices, notably cigarette and alcohol consumption. The risk of cervical cancer is linked to age at first intercourse and the number of sexual partners (and the risk of venereal transmission of an oncogenic virus). There is no escape. It seems that everything one does

vertical transmission of an oncogenic virus). There is no escape. It seems that everything one can enjoy life turns out to be illegal, immoral, or fattening, or-most disturbing-possibly carcinogenic.

## Age

In general, the frequency of cancer increases with age. Most cancer mortality occurs between age 40 and 75. The rising incidence with age may be explained by the accumulation of mutations with the emergence of malignant neoplasms (discussed later). The decline in immune competence with age is another factor.

Cancer causes slightly more than 10% of all deaths among children younger than 15 years (Chap 10). The most common childhood cancers are leukemia, tumors of the central nervous system, lymphomas, soft tissue sarcomas, and brain tumors. A study of several childhood tumors, particularly retinoblastoma and Wilms tumor, has provided novel insights into the mechanisms of malignant transformation.

## Heredity

The evidence now indicates that for many types of cancer, including the most common forms, the inheritance of a predisposing mutation is a major factor. Hereditary forms of cancer can be divided into three categories: inherited cancer syndromes, familial cancers, and sporadic cancers.

### Inherited Cancer Syndromes

**Table 6-3. Inherited Predisposition to Cancer**

<b>Inherited Cancer Syndromes (Autosomal Dominant)</b>	
Gene	Inherited Predisposition
<i>RB</i>	Retinoblastoma
<i>p53</i>	Li-Fraumeni syndrome (various tumors)
<i>p16INK4A</i>	Melanoma
<i>APC</i>	Familial adenomatous polyposis/colon cancer
<i>NF1, NF2</i>	Neurofibromatosis 1 and 2
<i>BRCA1, BRCA2</i>	Breast and ovarian tumors
<i>MEN1, RET</i>	Multiple endocrine neoplasia 1 and 2
<i>MSH2, MLH1, MSH6</i>	Hereditary nonpolyposis colon cancer
<i>PATCH</i>	Nevoid basal cell carcinoma syndrome
<b>Familial Cancers</b>	
Familial clustering of cases, but role of inherited predisposition not clear for each individual	
Breast cancer (not linked to <i>BRCA1</i> or <i>BRCA2</i> )	
Ovarian cancer	
Pancreatic cancer	
<b>Inherited Autosomal Recessive Syndromes of Defective DNA Repair</b>	
Xeroderma pigmentosum	
Ataxia-telangiectasia	
Bloom syndrome	
Fanconi anemia	

Inherited cancer syndromes include several well-defined cancers in which inheritance of a single mutation predisposes to developing a tumor. The predisposition to these tumors shows an autosomal dominant pattern of inheritance. The most striking example of this category is retinoblastoma. Approximately 40% of retinoblastomas are familial. As the *RB* gene has been implicated in the pathogenesis of this tumor. Carriers of this gene have a 10,000-fold increased risk of developing a second retinoblastoma, usually bilaterally. They also have a greatly increased risk of developing a second cancer. Familial adenomatous polyposis is another hereditary disorder marked by an extraordinarily high incidence of colon cancer. Individuals with an autosomal dominant mutation have, at birth or soon thereafter, innumerable polypoid adenomas of the colon. By age 50, they develop a carcinoma of the colon (see Table 6-3).



Tumors within this group often are associated with a specific marker phenotype. There may be metaplasia, as occurs in familial polyposis of the colon and in multiple endocrine neoplasia. Sometimes, certain tissues are not the target of transformation (e.g., Lisch nodules and café-au-lait spots in neurofibromatosis).

### *Familial Cancers*

Virtually all the common types of cancers that occur sporadically have been reported to occur in families. Examples include carcinomas of colon, breast, ovary, and brain. *Features that characterize familial cancers include occurrence in first-degree relatives of the index case, and sometimes multiple or bilateral tumors.* Familial cancers are often associated with marker phenotypes. For example, in contrast to the familial adenomatous polyposis syndrome, familial colorectal cancer often occurs in the absence of preexisting benign polyps. The transmission pattern of familial cancers is not clear. In general, sibling segregation analysis of large families usually reveals that predisposition to the tumors is dominant. As discussed later, certain familial cancers can be linked to the inheritance of

### *Autosomal Recessive Syndromes of Defective DNA Repair*

Besides the dominantly inherited precancerous conditions, a small group of autosomal recessive conditions are associated with chromosomal or DNA instability. One of the best-studied examples is xeroderma pigmentosum, in which patients are highly susceptible to skin cancer. Other familial disorders of DNA instability are described later.

In summary, no more than 5% to 10% of all human cancers fall into one of the three aforementioned categories. What is the influence of heredity in the large preponderance of malignant tumors? There is emerging evidence that the influence of genetic factors is subtle and indirect. The genotype may influence the likelihood of one's developing environmental cancer. For example, polymorphisms in drug-metabolizing enzymes confer genetic predisposition to lung cancer. Similarly, genetic predisposition to developing mesotheliomas (an asbestos-associated tumor) also has been known.

### **Acquired Preneoplastic Disorders**

In addition to the genetic influences described earlier, certain clinical conditions are well-recognized precursors of malignant neoplasia and are referred to as *preneoplastic disorders*. This designation is unfortunate because, in fact, although such conditions may increase the likelihood, in most instances cancer does not develop. Examples of preneoplastic conditions follow:

Persistent regenerative cell replication (e.g., squamous cell carcinoma in the margins of a chronic skin wound; hepatocellular carcinoma in cirrhosis of the liver) Hyperplastic and dysplastic polyps of the colon (e.g., adenomatous polyps) Atypical endometrial hyperplasia; bronchogenic carcinoma in the dysplastic bronchial mucosa of heavy smokers Chronic atrophic gastritis (e.g., gastric carcinoma in pernicious anemia or following chronic infection) Chronic ulcerative colitis (e.g., an increased incidence of colorectal carcinoma in long-standing disease) Oral cavity, vulva, or penis (e.g., increased risk of squamous cell carcinoma) Villous adenoma of the colon (e.g., increased risk of transformation to colorectal carcinoma)

In this context it may be asked, "What is the risk of malignant change in a benign neoplasm?" or, "What is the risk of malignant change in a precancerous condition?" In general the answer is no, but inevitably there are exceptions, and perhaps it is not surprising that a particular tumor is associated with a particular level of risk, ranging from high to virtually nonexistent. For example, a villous adenoma of the colon can undergo malignant transformation in 50% of cases; in contrast, malignant change is extremely rare in a benign uterine fibroid.

## **SUMMARY**

### **Epidemiology of Cancer**

The incidence of cancer varies with age, race, geographic factors, and genetic factors. The most common cancers are most common at the two extremes of age. The geographic variation reflects differences in environmental exposures. Most cancers are sporadic, but some are familial. The inheritance of familial cancers may be autosomal dominant or autosomal recessive. The inheritance of a germ-line mutation of cancer suppressor genes, whereas

associated with inherited defects in DNA repair. Familial cancers tend to be  
in life than their sporadic counterparts.



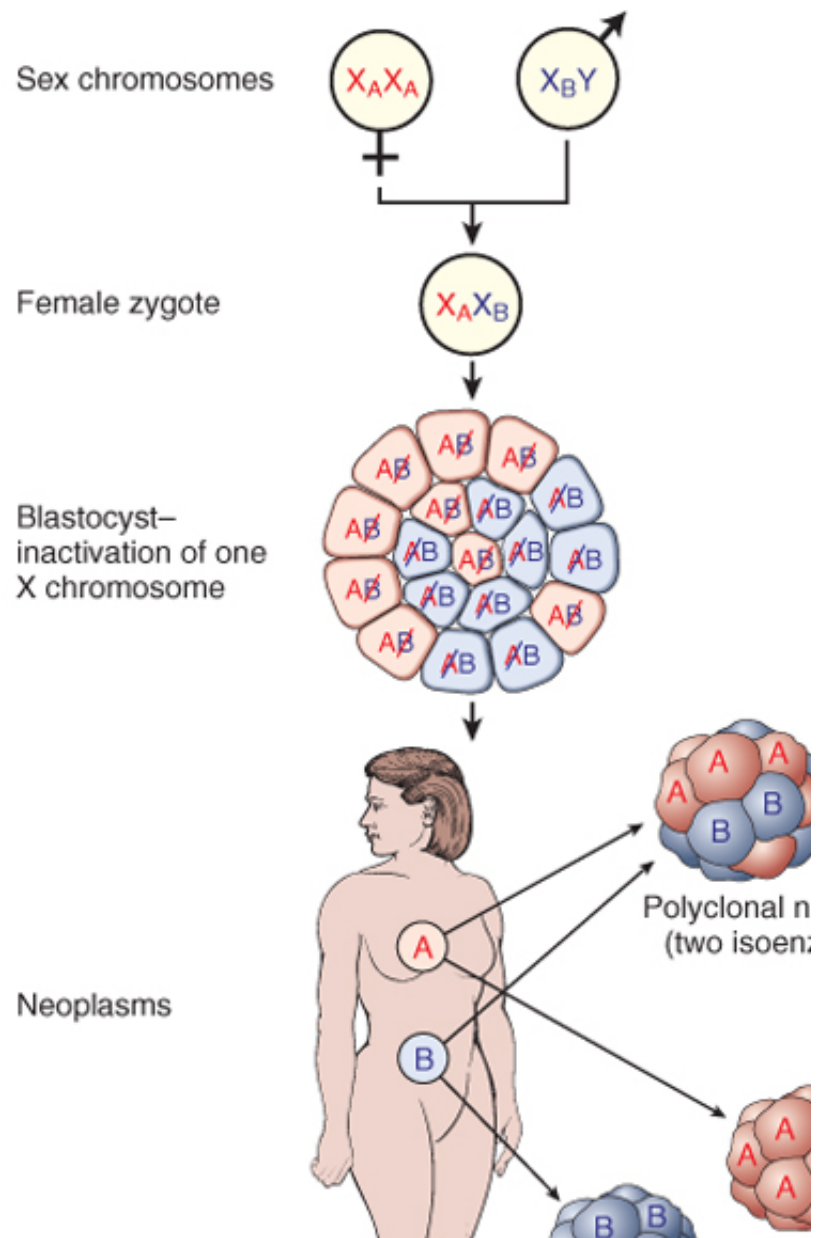
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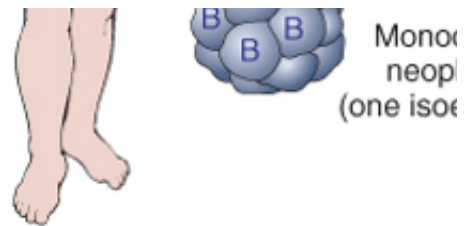
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## CARCINOGENESIS: THE MOLECULAR BASIS OF CANCER

It could be argued that the proliferation of literature on the molecular basis of cancer has outpaced that of tumors. It is easy to get lost in the growing forest of information. First, we list some fundamentals of the genetic basis of cancer.

*Nonlethal genetic damage lies at the heart of carcinogenesis.* Such genetic damage (or mutation) from environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line (implies that a tumor mass results from the clonal expansion of a single progenitor cell that has inherited the mutation (i.e., is monoclonal). This expectation has been realized in most tumors that have been analyzed. Clonality can be demonstrated in women who are heterozygous for polymorphic X-linked markers, such as the enzyme glucose-6-phosphate dehydrogenase (G6PD) deficiency. The principle underlying such an analysis is illustrated





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Figure 6-14 Diagram depicting the use of X-linked isoenzyme cell markers as evidence of the monoclonality of neoplasms. Females are mosaics with two cell populations (with glucose-6-phosphate dehydrogenase isoenzyme A or B in this case). If neoplasms that are heterozygous for X-linked markers are analyzed, they are made up of cells that contain the active maternal (X) or paternal (X) allele only, not both. Currently, X-linked molecular markers are used more commonly than isoenzymes.

*Four classes of normal regulatory genes—growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (i.e., apoptosis), and genes involved in DNA repair—are the principal classes of genes that, when altered, confer upon tumor cells a growth and survival advantage. Collectively the genetic alterations in tumor cells confer upon them growth and survival advantage. The following discussion follows.*

Mutant alleles of proto-oncogenes are called oncogenes. They are considered dominant because a single copy of a mutant allele can lead to cellular transformation. In contrast, typically both normal alleles of tumor suppressor genes must be lost for a cell to undergo transformation, so this family of genes is sometimes referred to as recessive oncogenes. However, recent work has shown that loss of a single allele of a tumor suppressor gene can promote transformation (haploinsufficiency), so some tumor suppressor genes behave as dominant, as are proto-oncogenes, or they may behave as tumor suppressor genes. Tumor suppressor genes are divided into two general groups, promoters and caretakers. Promoters are the traditional tumor suppressor genes, and their mutation leads to transformation by releasing the brakes on cellular proliferation. Caretaker genes ensure the integrity of the genome, such as DNA repair. Mutation of caretaker genes does not directly lead to transformation but can lead to proliferation or apoptosis. Instead, DNA repair genes affect cell proliferation or survival indirectly by repairing nonlethal damage in other genes, including proto-oncogenes, tumor suppressor genes, and caretaker genes. Disability in the DNA repair genes can predispose cells to widespread mutations in the genome and cells with mutations in caretaker genes are said to have developed a *mutator phenotype*.

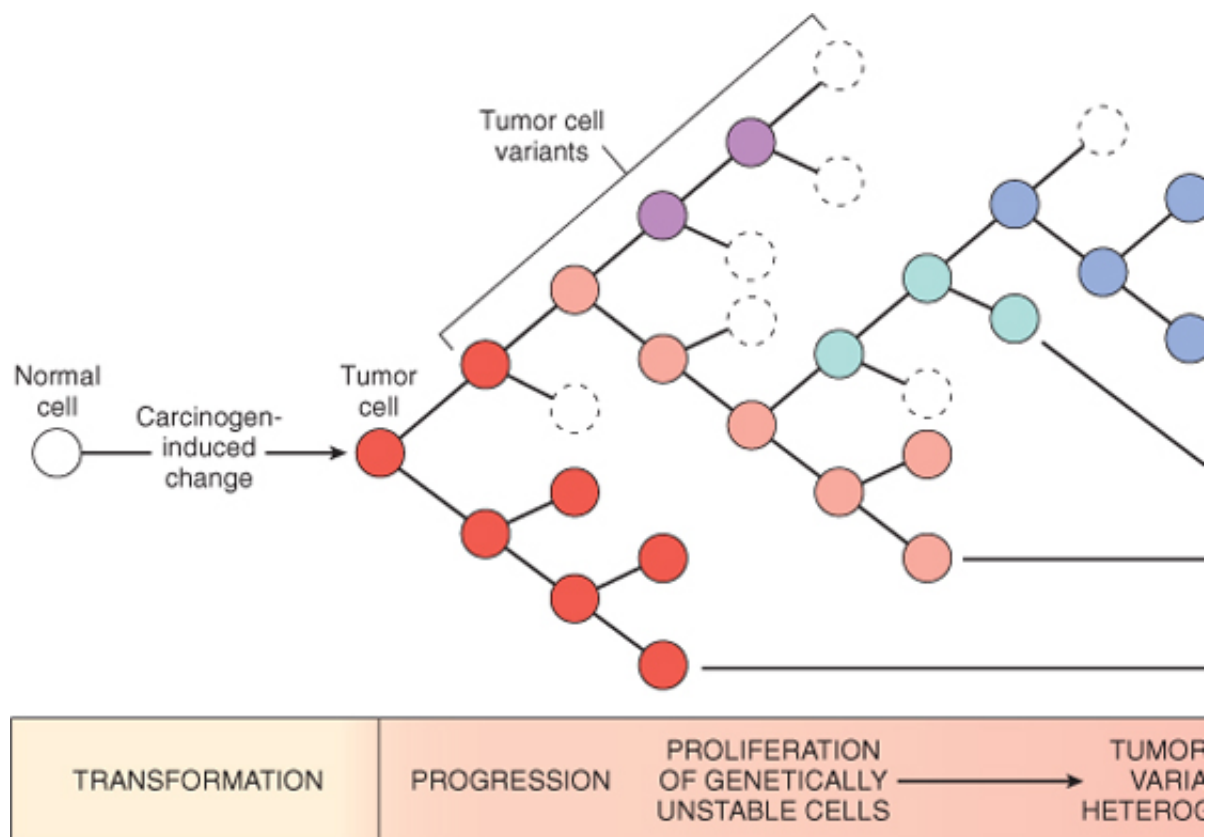
*Carcinogenesis is a multistep process at both the phenotypic and the genetic levels, resulting from the accumulation of multiple mutations. As discussed earlier, malignant neoplasms have several phenotypic attributes, such as excessive growth, local invasion, and the ability to form distant metastases. Furthermore, it is well established that over a period of time, malignant neoplasms acquire greater malignant potential. This phenomenon is referred to as tumor progression and is related to increasing tumor size. Careful clinical and experimental studies reveal that increasing malignancy is often associated with increasing tumor size. At the molecular level, tumor progression and associated heterogeneity most likely result from multiple mutations in different cells, generating subclones with different characteristics (Fig. 6-15) such as ability to invade, resistance to apoptosis, karyotype, hormonal responsiveness, and susceptibility to anti-neoplastic drugs. Some of the mutations that lead to tumor growth by affecting proto-oncogenes or cancer suppressor genes. Even though most malignant tumors are clinically evident, their constituent cells are extremely heterogeneous. During progression, both immune and nonimmune selection pressures. For example, cells that are highly antigenic are destroyed by the immune system, while cells with reduced growth factor requirements are positively selected. A growing tumor, therefore, tends to be "selected for the odds" and are adept at survival, growth, invasion, and metastasis.*

## SUMMARY

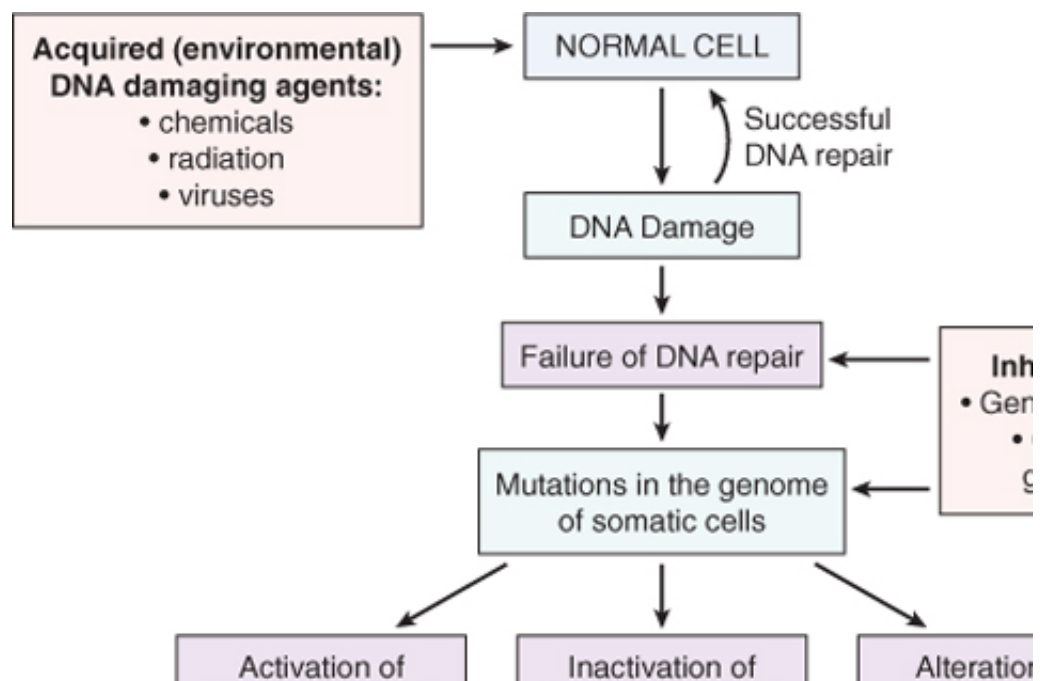
### Overview of Carcinogenesis

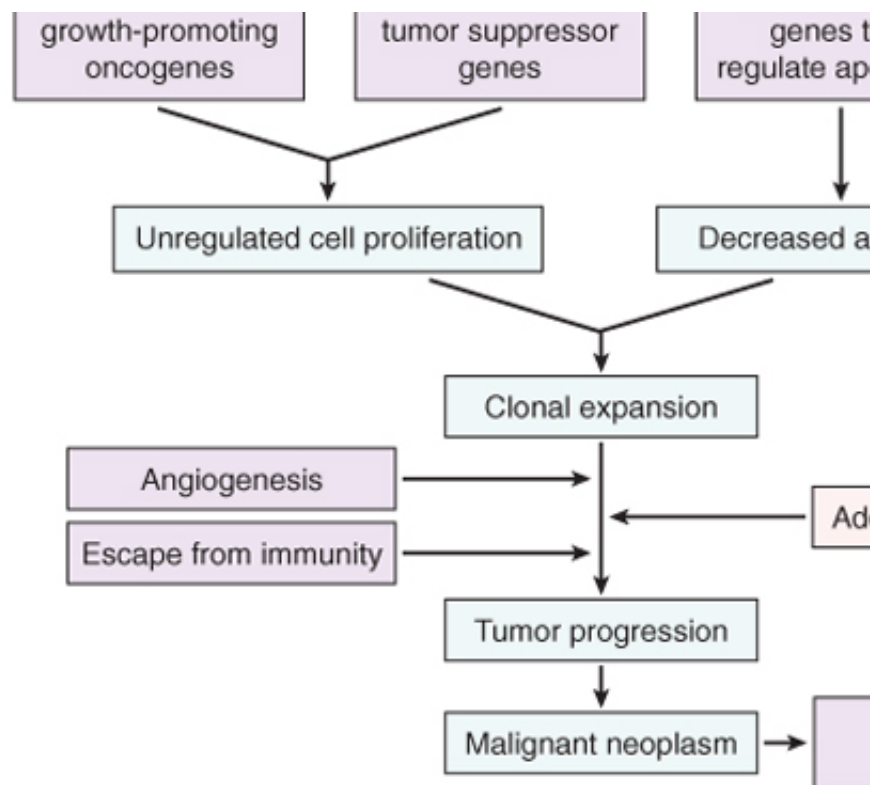
Tumors arise from clonal growth of cells that have incurred mutations in four classes of genes: growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes, genes that regulate apoptosis, and genes involved in DNA repair. Mutation in no single gene is sufficient to cause a cell to become malignant. The phenotypic attributes characteristic of malignancy develop when multiple mutations in multiple genes accumulate. The stepwise accumulation of mutations and the resulting changes in the cell are referred to as tumor progression.





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 Figure 6-15 Tumor progression and generation of heterogeneity. New subclones arise from the descendants of the  
 With progression the tumor mass becomes enriched for variants that are more adept at evading host defen





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Figure 6-16 Flow chart depicting a simplified scheme of the molecular basis of cancer.

With this overview (Fig. 6-16), we can now address in detail the molecular pathogenesis of cancer that inflict genetic damage. In the past 20 years hundreds of cancer-associated genes have been commonly mutated; others, such as *c-ABL*, are affected only in certain leukemias. Each cancer gene represents a dysregulation of which contributes to the origin or progression of malignancy. It is best therefore to consider the context of seven fundamental changes in cell physiology that together dictate the malignant phenotype. These are illustrated in Figure 6-17:

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory signals
3. Evasion of apoptosis
4. Limitless replicative potential (i.e., overcoming cellular senescence and avoiding mitotic catastrophe)
5. Development of sustained angiogenesis
6. Ability to invade and metastasize
7. Genomic instability resulting from defects in DNA repair

Mutations in genes that regulate some or all of these cellular traits are seen in every cancer, and this forms the basis of the discussion of the molecular origins of cancer. In the ensuing discussion it should be noted that gene products are not (e.g., *RB* gene and RB protein).

### Self-Sufficiency in Growth Signals

Genes that promote autonomous cell growth in cancer cells are called *oncogenes*. They are derived from normal genes and are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals. *Oncoproteins*, resemble the normal products of proto-oncogenes except that oncoproteins are deviant. Because the production in the transformed cells does not depend on growth factors or other external signals, to understand the nature and functions of oncoproteins, it is necessary to review briefly the sequence of events that

these were introduced in [Chapter 3](#). Under physiologic conditions, cell proliferation can be readily

The binding of a growth factor to its specific receptor on the cell membrane transient and ligand receptor, which in turn activates several signal-transducing proteins on the inner leaflet of the plasma membrane. The transduced signal across the cytosol to the nucleus via second messengers or a cascade of protein kinases, leading to the activation of nuclear regulatory factors that initiate DNA transcription and progression through the cell cycle, resulting ultimately in cell division.

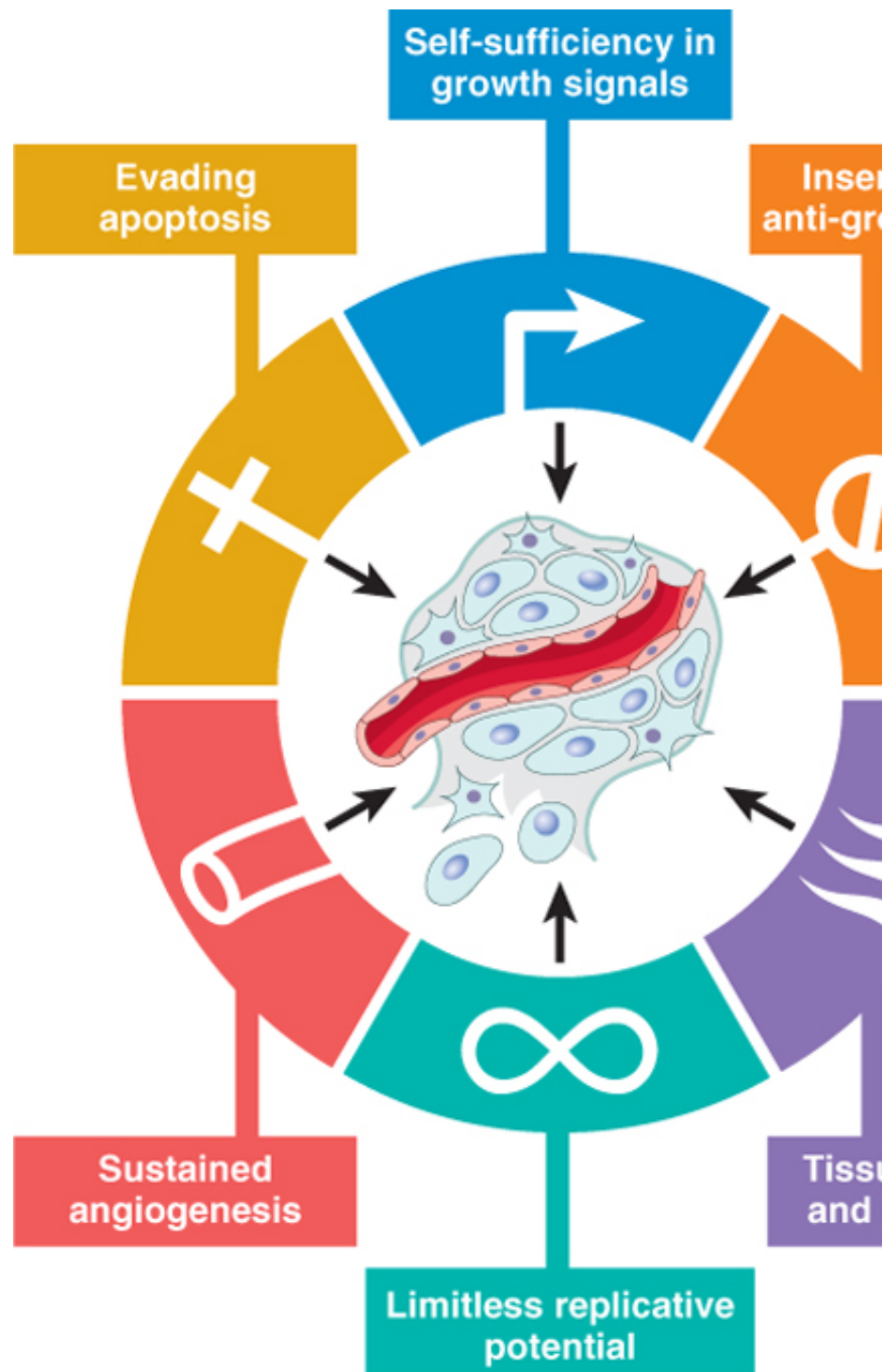


Figure 6-17 Six hallmarks of cancer. Most cancer cells acquire these properties during their development, typically during embryonic development. Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100:57, 2000

With this background we can identify the strategies used by cancer cells to acquire self-sufficiency in growth factor signaling, on the basis of their role in the signal transduction cascade and cell cycle regulation. Indeed, each hallmark is a corruption by cancer cells.

### Growth Factors

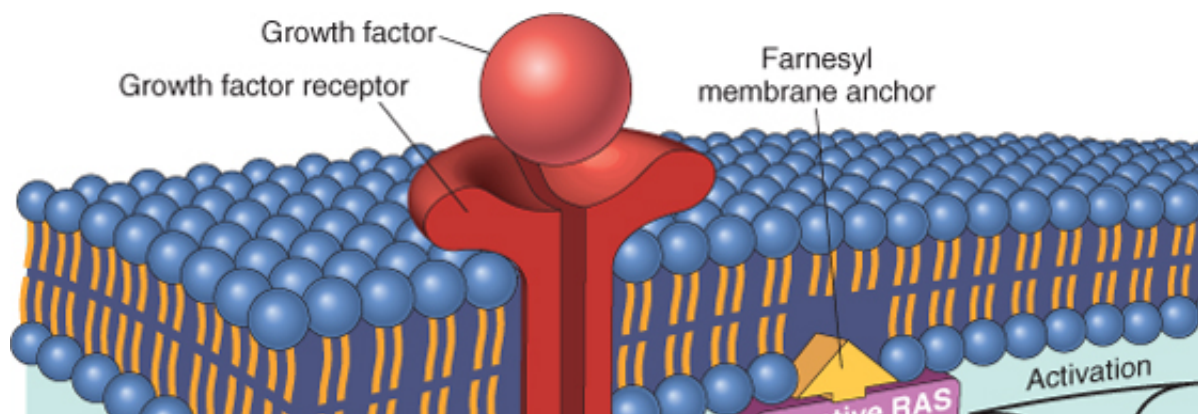
All normal cells require stimulation by growth factors to undergo proliferation. Most soluble growth factors act on a neighboring cell to stimulate proliferation (paracrine action). Many cancer cells acquire growth factor self-sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive. For example, some cancer cells produce and express the PDGF receptor, and many sarcomas make both the ligand and its receptor. Similar autocrine loops are fairly common in many types of cancer. Genes that encode growth factors (e.g., *hst-1* and *FGF3*) have been detected in several gastrointestinal and breast tumors; *FGF-2* is overexpressed in normal melanocytes. Hepatocyte growth factor (HGF) and its receptor c-Met are both overexpressed in some cancers. In many instances the growth factor gene itself is not altered or mutated, but the products of other genes that promote overexpression of growth factor genes and the subsequent development of an autocrine loop.

### Growth Factor Receptors

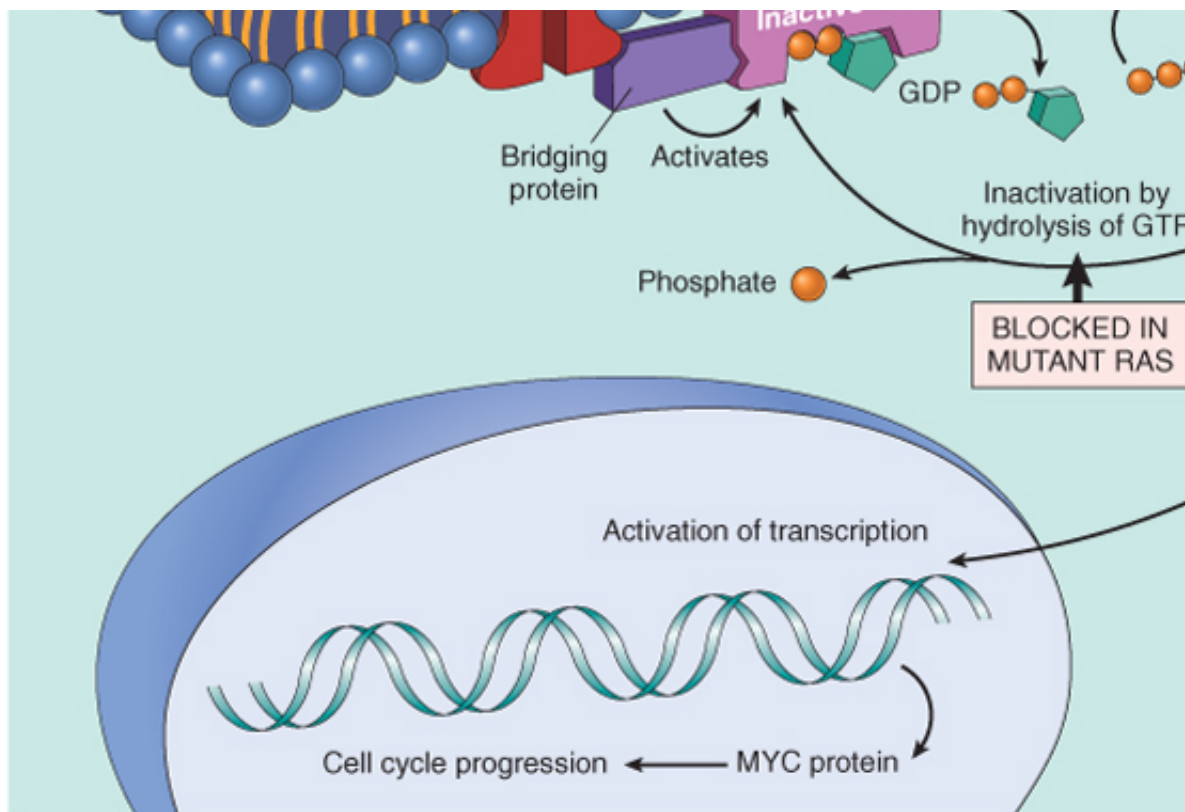
The next group in the sequence of signal transduction is growth factor receptors, and several oncogenes have been identified. Overexpression or mutation of growth factor receptors have been identified. Mutant receptors that are constitutively active in the absence of the growth factor in the environment. More common than mutant receptors, which can render cancer cells hyper-responsive to levels of the growth factor that would normally be non-effective, are receptors that are overexpressed. The best-documented examples of overexpression involve the epidermal growth factor (EGF) receptor, which is overexpressed in 80% of squamous cell carcinomas of the lung, 50% or more of glioblastomas, and 30% or more of cancers of the head and neck. A related receptor, called *HER2/NEU (ERBB2)*, is amplified in 25% to 30% of breast cancers of the lung, ovary, and salivary glands. These tumors are exquisitely sensitive to the mitogenic effects of the growth factor. A high level of *HER2/NEU* protein in breast cancer cells is a harbinger of poor prognosis. The significance of *HER2/NEU* in breast cancer is illustrated dramatically by the clinical benefit derived from blocking the extracellular domain of the receptor with anti-*HER2/NEU* antibodies. Treatment of breast cancer with anti-*HER2/NEU* antibody is an elegant application of targeted therapy.

### Signal-Transducing Proteins

A relatively common mechanism by which cancer cells acquire growth autonomy is mutations in genes that encode the signaling pathways downstream of growth factor receptors. These signaling molecules couple the activated growth factor receptors and transmit them to the nucleus, either through second messenger systems or by direct phosphorylation and activation of signal transduction molecules. Two important members in this class are *RAS* and *RAF*, which are discussed briefly.







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Figure 6-18 Model for action of *RAS* genes. When a normal cell is stimulated through a growth factor receptor, in bound state. Activated *RAS* recruits *RAF-1* and stimulates the *MAP-kinase* pathway to transmit growth-promoting signals to several targets of the activated *RAS* pathway. The mutant *RAS* protein is permanently activated because of inability to hydrolyze GTP to GDP. The anchoring of *RAS* to the cell membrane by the farnesyl moiety can inhibit *RAS* action.

*RAS* is the most commonly mutated proto-oncogene in human tumors. Indeed, approximately 30% of the *RAS* gene, and the incidence is even higher in some specific cancers (e.g., colon cancer). *RAS* is a member of a family of small G proteins that bind guanosine nucleotides (guanosine triphosphate [GTP]), similar to the larger trimolecular G proteins. Normal *RAS* proteins flip back and forth between an active state and a quiescent state. *RAS* proteins are inactive when bound to GDP; stimulation of cells by growth factors causes exchange of GDP for GTP and subsequent conformational changes that generates active *RAS* (Fig. 6-18). The activated *RAS* protein recruits and activates several downstream effectors, such as the *RAF-mitogen-activated protein (MAP) kinase* pathway, which transmits signals for cell proliferation. The excited signal-emitting stage of the normal *RAS* protein is short-lived because of its intrinsic guanosine triphosphatase (GTPase) activity hydrolyzes GTP to GDP, releasing a phosphate group and returning the protein to its quiescent inactive state. The GTPase activity of activated *RAS* protein is magnified dramatically by GAPs, which act as molecular brakes that prevent uncontrolled *RAS* activation by favoring hydrolysis of GTP to GDP.

The *RAS* gene is most commonly activated by point mutations. Molecular analyses of *RAS* mutations have identified several residues either within the GTP-binding pocket or the enzymatic region essential for GTP hydrolysis that interfere with GTP hydrolysis that is essential to convert *RAS* into an inactive form. *RAS* is thus trapped in the active state, and the cell is forced into a continuously proliferating state. It follows from this scenario that the cellular growth-promoting effect of *RAS* would be mimicked by mutations in the GAPs that fail to restrain normal *RAS* proteins. Indeed, *ras* is associated with familial neurofibromatosis type 1 (Chapter 23).

In addition to *RAS*, several non-receptor-associated tyrosine kinases function as signal transducers in the most well defined with respect to carcinogenesis. The *ABL* proto-oncogene has tyrosine kinase activity and a negative regulatory domain. In chronic myeloid leukemia and certain acute leukemias, this activity is constitutively activated by a reciprocal translocation between chromosomes 9 and 22, where it fuses with part

translocated from its normal abode on chromosome 9 to chromosome 22, where it fuses with part of the *BCR* gene. The *BCR-ABL* hybrid protein has potent, unregulated tyrosine kinase activity, which activates the *RAF* cascade. Other studies have revealed a completely novel function of *ABL* in oncogenesis. In the nucleus, where its role is to promote apoptosis of cells that suffer DNA damage. This is analogous to the function of the *p53* protein (see later). The *BCR-ABL* gene cannot perform this function, because it is retained in the cytoplasm as a fusion protein. Thus, a cell with *BCR-ABL* fusion gene is dysregulated in two ways: inappropriate tyrosine kinase activity, while simultaneously apoptosis is impaired.

The crucial role of *BCR-ABL* in transformation has been confirmed by the dramatic clinical response of leukemia after therapy with an inhibitor of the *BCR-ABL* fusion kinase called **imatinib mesylate**<sup>®</sup> (a product of rational drug design emerging from an understanding of the molecular basis of cancer).

### **Nuclear Transcription Factors**

Ultimately, all signal transduction pathways enter the nucleus and have an impact on a large bank of genes that drive cells' orderly advance through the mitotic cycle. Indeed, the ultimate consequence of signaling through inappropriate and continuous stimulation of nuclear transcription factors that drive growth-promoting genes to occur as a consequence of mutations affecting genes that regulate transcription of DNA. A host of *MYC*, *MYB*, *JUN*, *FOS*, and *REL* oncogenes, function as transcription factors that regulate the expression of genes as cyclins. Of these, the *MYC* gene is involved most commonly in human tumors. The *MYC* protein is induced rapidly when quiescent cells receive a signal to divide. In the basal level when the cell cycle begins. In contrast, oncogenic versions of the *MYC* gene are associated with overexpression, contributing to sustained proliferation.

The *MYC* protein can either activate or repress the transcription of other genes. Those activated by *MYC* include the CDK inhibitors (CDKIs). Thus, *MYC* promotes tumorigenesis by increasing expression of genes that drive the cell cycle and repressing genes that slow or prevent progression through the cell cycle. A mutation resulting from a t(8;14) translocation occurs in Burkitt lymphoma, a B-cell tumor. *MYC* is also amplified in other cancers; the related *N-MYC* and *L-MYC* genes are amplified in neuroblastomas and small-cell lung cancers.

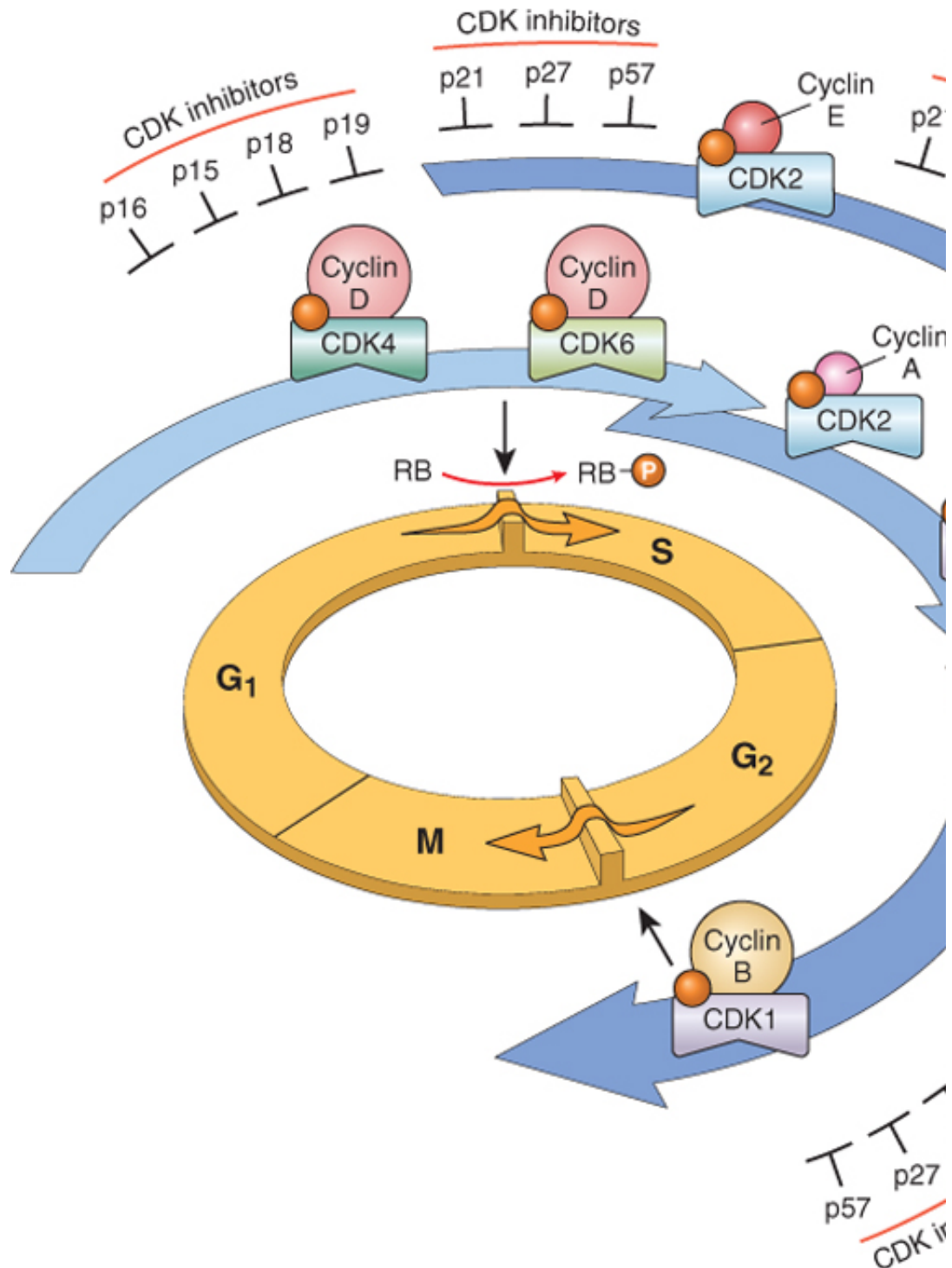
### **Cyclins and Cyclin-Dependent Kinases (CDKs)**

The ultimate outcome of all growth-promoting stimuli is the entry of quiescent cells into the cell cycle. The genes that drive the cell cycle become dysregulated by mutations or amplification. As alluded to earlier, the progression of cells through the various phases of the cell cycle is orchestrated by CDKs, which are activated by the cyclic nature of their production and degradation. The CDK-cyclin complexes phosphorylate proteins that drive the cell cycle. On completion of this task, cyclin levels decline rapidly. More than 15 cyclins and B appear sequentially during the cell cycle and bind to one or more CDK. The cell cycle may be thought of as a series of laps, each lap is regulated by a distinct set of cyclins, and as one set of cyclins leaves the track, the next set enters.

With this background it is easy to appreciate that mutations that dysregulate the activity of cyclins and CDKs are common in cancer. Mishaps affecting the expression of cyclin D or CDK4 seem to be a common event in neoplastic transformation. Cyclin D is overexpressed in many cancers, including those affecting the breast, esophagus, liver, and a subset of colorectal cancers. A mutation of the *CDK4* gene occurs in melanomas, sarcomas, and glioblastomas. Mutations affecting cyclin B and CDK2 are much less frequent than those affecting cyclin D/CDK4.

While cyclins arouse the CDKs, their inhibitors (CDKIs), of which there are many, silence the CDK activity. One family of CDKIs, composed of three proteins, called p21 [CDKN1A], p27 [CDKN1B], and p57 [CDKN1C], act broadly, whereas the other family of CDKIs has selective effects on cyclin D/CDK4 and cyclin D/Cdk2 (p15 [CDKN2B], p16 [CDKN2A], p18 [CDKN2C], and p19 [CDKN2D]) are sometimes called INK4 inhibitors. The p16 INK4A is down-regulated by mitogenic signaling pathways, thus promoting the progression of the cell cycle. p21 [CDKN1A], a CDKI that inhibits cyclin E, is expressed throughout G<sub>1</sub>. Mitogenic signals obtund p21 and thus allowing the cell cycle to proceed. Interestingly, the *CDKN2A* gene locus encodes two protein products: the p16 INK4A and p14ARF. Both block cell cycle progression but have different mechanisms of action: p16 INK4A blocks cyclin D-CDK4 complex, whereas p14ARF activates the p53 pathway. Thus, both proteins function as tumor suppressors, and deletion of this locus, frequent in many tumor types, is a common event. The CDKIs are frequently mutated or otherwise silenced in many human malignancies.

associated with 25% of melanoma-prone kindreds. Somatically acquired deletion or inactivation of *p53* is found in 50% to 70% of colon carcinomas, 40% to 70% of glioblastomas, 50% of esophageal cancers, and 20% of non-small-cell lung and bladder cancers.



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Figure 6-19 Schematic illustration of the role of cyclins, CDKs, and CDKIs in regulating the cell cycle. The shaded areas indicate the phases of the cell cycle during which specific cyclin-CDK complexes are active. As illustrated, cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 are active in the G<sub>1</sub> phase, leading to the phosphorylation of the RB protein (pRB). Cyclin A-CDK2 and cyclin A-CDK1 are active in the S phase. Cyclin B-CDK1 is active in the M phase, leading to the phosphorylation of the histone H1 protein (pH1).

families of CDK inhibitors can block activity of CDKs and progression through the cell cycle. The so-called INK4 inhibitors bind to cyclin D-CDK4 and cyclin D-CDK6. The other family of three inhibitors, p21, p27, and p

## SUMMARY

### Oncogenes that Promote Unregulated Proliferation (Self-sufficiency in Growth)

*Proto-oncogenes*: normal cellular genes whose products promote cell proliferation

*Oncogenes*: mutant versions of proto-oncogenes that function autonomously without normal growth-promoting signals

Oncogenes can promote uncontrolled cell proliferation by several mechanisms:

- Stimulus-independent expression of growth factor and its receptor, setting up constitutive proliferation

  - PDGF-PDGF-receptor in brain tumors

- Mutations in genes encoding growth factor receptors, leading to overexpression and constitutive signaling by the receptor (e.g., EGF receptors)

  - EGF-receptor family members, including HER2/NEU (breast, lung, and colon)

- Mutations in genes encoding signaling molecules

  - RAS is commonly mutated in human cancers; normally flips between inactive GDP-bound and active GTP-bound state; mutations block hydrolysis of GTP to GDP, leading to constitutive signaling
  - Fusion of ABL tyrosine kinase with BCR protein in certain leukemias, forming a hybrid protein with constitutive kinase activity

- Overproduction or unregulated activity of transcription factors

  - Translocation of MYC in some lymphomas leads to overexpression and constitutive expression of its target genes controlling cell cycling and survival

- Mutations that activate cyclin genes or inactivate normal regulators of cyclin-dependent kinases

  - Complexes of cyclins with cyclin-dependent kinases (CDKs) drive the cell cycle by phosphorylating various substrates; CDKs are controlled by inhibitors. Mutations encoding cyclins, CDKs, and CDK inhibitors result in uncontrolled cell growth. Mutations are found in a wide variety of cancers including melanomas, colorectal cancer, and pancreatic cancer.

## Insensitivity to Growth-Inhibitory Signals

Isaac Newton predicted that every action has an equal and opposite reaction. Although Newton's law holds true for cell growth. Whereas oncogenes encode proteins that promote cell growth, the protein products of tumor suppressor genes act as brakes to cell proliferation. Disruption of such genes renders cells refractory to growth inhibition and promotes cell growth. In this section we describe tumor suppressor genes, their products, and possible mechanisms by which they contribute to unregulated cell growth.

We begin our discussion with the retinoblastoma (*RB*) gene, the first and prototypic cancer suppressor gene. In the history of many advances in medicine, the discovery of cancer suppressor genes was accomplished by the study of the retinoblastoma, an uncommon childhood tumor. Approximately 60% of retinoblastomas are sporadic, the predisposition to develop the tumor being transmitted as an autosomal dominant trait. To account for the occurrence of an identical tumor, Knudson, in 1974, proposed his now famous *two-hit* hypothesis, as follows:

Two mutations (*hits*) are required to produce retinoblastoma. These involve the *RB* gene, the normal alleles of the *RB* locus must be inactivated (two hits) for the development of retinoblastoma. Children inherit one defective copy of the *RB* gene in the germ line; the other copy is normal. In the normal *RB* gene is lost in retinoblasts as a result of somatic mutation. Because in retinoblastoma one mutation is required for expression of the disease, the familial transmission follows an auto



mutation is required for expression of the disease, the familial transmission follows an autosomal dominant pattern. In sporadic cases, both normal *RB* alleles are lost by somatic mutation in one of the retinoblastoma cells. A cell that has lost both of the normal copies of the *RB* gene becomes cancerous.

Although the loss of normal *RB* genes was discovered initially in retinoblastomas, it is now evident that the loss of normal *RB* genes is a fairly common event in several tumors, including breast cancer, small-cell cancer of the lung, and osteosarcoma. Retinoblastoma also is at greatly increased risk of developing osteosarcomas and some soft tissue sarcomas.

At this point, we should clarify some terminology. A cell heterozygous at the *RB* locus is not neoplastic. A cell becomes homozygous for the mutant allele or, in other words, loses heterozygosity of the normal allele.

The signals and signal-transducing pathways for growth inhibition are much less well understood than those for growth promotion. Nevertheless, it is reasonable to assume that, similar to mitogenic signals, growth-inhibitory signals use receptors, signal transducers, and nuclear transcription regulators to accomplish their effects. The *RB* gene encodes various components of this growth-inhibitory pathway.

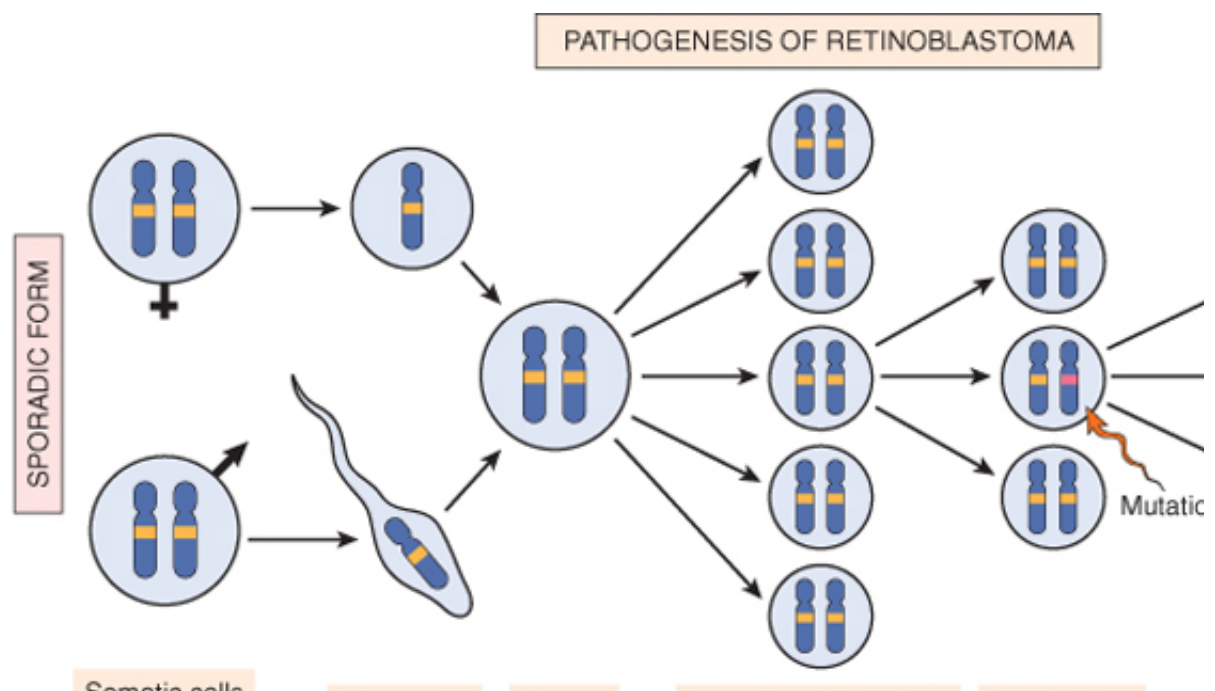
In principle, antigrowth signals can prevent cell proliferation by two complementary mechanisms. First, they can induce cells to enter G<sub>0</sub> (quiescence), where they remain until external cues prod their reentry into the proliferative pool. Second, they can induce postmitotic, differentiated cells to lose replicative potential. It is useful to begin our discussion of tumor suppressor genes by focusing initially on the *RB* gene, the prototypic tumor suppressor gene.

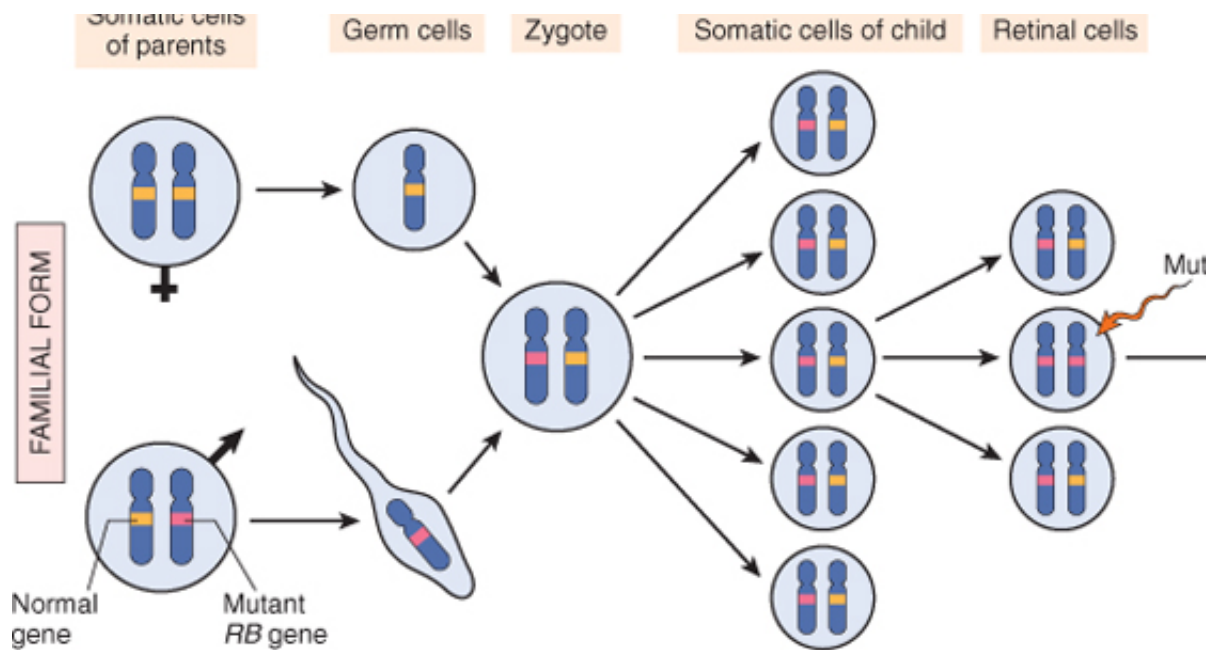
## SUMMARY

### Insensitivity to Growth-Inhibitory Signals

Tumor suppressor genes encode proteins that inhibit cellular proliferation by inducing cells to enter G<sub>0</sub> (quiescence) or by inducing postmitotic, differentiated cells to lose replicative potential. Unlike oncogenes, both copies of the gene must be lost for tumor development. In cases with familial predisposition to develop retinoblastoma, individuals inherit one defective (nonfunctional) copy of a tumor suppressor gene. In sporadic cases both copies are lost through somatic mutation.

## *RB* Gene and Cell Cycle





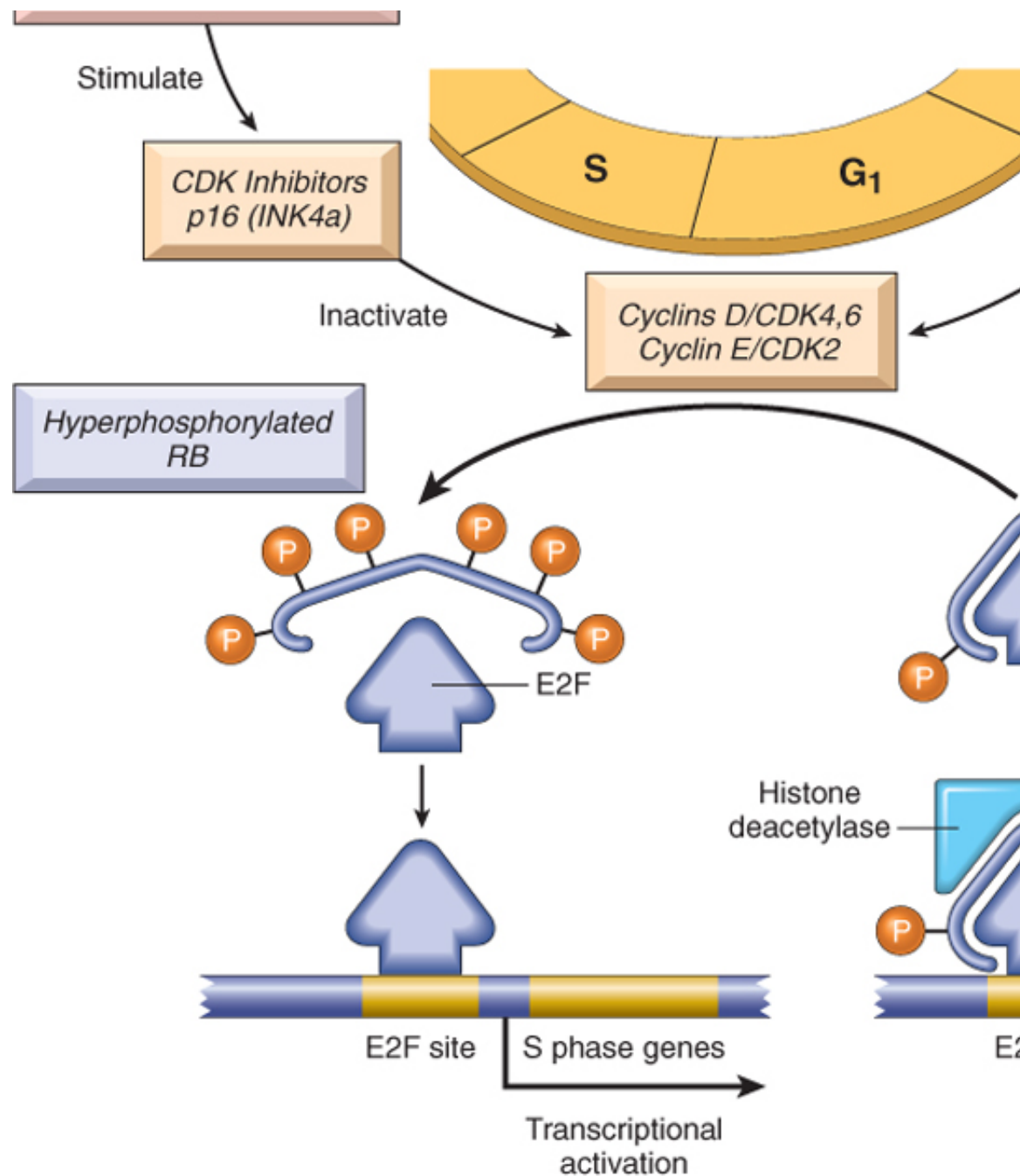
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Figure 6-20 Pathogenesis of retinoblastoma. Two mutations of the *RB* locus on chromosome 13q14 lead to neoplasia. In the familial form, all somatic cells inherit one mutant *RB* gene from a carrier parent. The second mutation affects the *RB* locus in a retinal cell. In the sporadic form, both mutations at the *RB* locus are acquired by the retinal cell.

Much is known about the *RB* gene, because this was the first tumor suppressor gene discovered. The protein that is expressed in every cell type examined, where it exists in an *active hypophosphorylated state*. The importance of RB lies in its enforcement of  $G_1$ , or the gap between mitosis (M) and DNA replication. In two gaps are incorporated into the cell cycle: Gap 1 ( $G_1$ ) between mitosis (M) and DNA replication (S) and mitosis (M) (see Fig. 6-19). Although each phase of the cell cycle circuitry is important, the  $G_1$  to S transition is believed to be an extremely important checkpoint in the cell cycle clock. Once cells cross this checkpoint, they are obligated to complete mitosis. In  $G_1$ , however, cells can exit the cell cycle into quiescence, or permanently, called senescence. In  $G_1$ , therefore, diverse signals are integrated to regulate the cell cycle, exit the cell cycle and differentiate, or die. RB is a key node in this decision process. As a tumor suppressor player, we must review the mechanisms that enforce the  $G_1$  phase.

The initiation of DNA replication requires the activity of cyclin E/CDK2 complexes, and expression of a family of transcription factors. Early in  $G_1$ , RB is in its hypophosphorylated active form, and it binds to transcription factors, preventing transcription of cyclin E. Hypophosphorylated RB blocks E2F-mediated transcription (Fig. 6-21). First, it sequesters E2F, preventing it from interacting with other transcriptional activators and chromatin remodeling proteins, such as histone deacetylases and histone methyltransferases, which bind to the promoters of genes that are changed upon mitogenic signaling. Growth factor signaling leads to cyclin D expression and activation of CDK4/6. These complexes phosphorylate RB, inactivating the protein and releasing E2F to induce target gene expression. Cyclin E then stimulates DNA replication and progression through the cell cycle. When the cells exit the cell cycle without additional growth factor stimulation. During the ensuing M phase, the phosphate groups are removed by phosphatases, regenerating the hypophosphorylated form of RB.

GROWTH INHIBITORS  
(TGF- $\beta$ , p53, others)



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Figure 6-21 The role of RB in regulating the G<sub>1</sub>-S checkpoint of the cell cycle. Hypophosphorylated RB in complex recruits chromatin remodeling factors (histone deacetylases and histone methyltransferases), and inhibits transcription of S phase genes. When RB is phosphorylated by the cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 complex, it releases E2F, which activates transcription of S-phase genes. The phosphorylation of RB is inhibited by CDKIs, because they inactivate the cyclin-CDK complex. Dysregulation of the G<sub>1</sub>-S checkpoint as a result of mutation in one of four genes that regulate the phosphorylation of RB (p16, p15, p18, and p19) and CDKN2A [p16]. EGF, epidermal growth factor; PDGF, platelet-derived growth factor.

E2F is not the sole target of RB. The versatile RB protein has been shown to bind to a variety of other proteins involved in cell differentiation. For example, RB stimulates myocyte-, adipocyte-, melanocyte-, and macrophage-specific gene expression. The RB protein pathway couples control of cell cycle progression at G<sub>1</sub> with differentiation, which may explain how cells exit the cell cycle. In addition to these dual activities, RB can also induce senescence, discussed in the next section.

Given that RB is central to the control of the cell cycle, one may ask why RB is not mutated in every cancer. The answer lies in the fact that RB is a tumor suppressor gene, and its mutation is a common event in many types of cancer, including retinoblastoma, osteosarcoma, and small cell lung cancer.

control RB phosphorylation can mimic the effect of *RB* loss; such genes are mutated in many cancers. For example, mutational activation of CDK4 or overexpression of cyclin D would favor cell proliferation and inactivation. Indeed, cyclin D is overexpressed in many tumors because of gene amplification and overexpression. Mutations of CDKIs also would drive the cell cycle by unregulated activation of cyclins and CDKs. As mentioned, *p16* is an extremely common target of deletion or mutational inactivation in human tumors.

*The emerging paradigm is that loss of normal cell cycle control is central to malignant transformation. Key regulators of the cell cycle (*CDKN2A*, cyclin D, *CDK4*, *RB*) is mutated in most human cancers.* For several oncogenic animal and human DNA viruses seem to act, in part, by neutralizing the growth-inhibitory activity of RB. For example, SV40 and polyomavirus large-T antigens, adenovirus E1A protein, and human papillomavirus (HPV) E7 bind to and inactivate the hypophosphorylated form of RB. The RB protein, unable to bind to the E2F transcription factors, is released, and the cell cycle is driven forward. The ability to be inhibited by antigrowth signals that funnel through the RB nexus is a critical feature of normal cells.

## SUMMARY

### ***RB Gene and Cell Cycle***

RB exerts antiproliferative effects by controlling the G<sub>1</sub>-to-S transition of the cell cycle. In its active form RB is hypophosphorylated and binds to E2F transcription factor. This inhibits transcription of genes like cyclin E that are needed for DNA replication, and thus cell growth. In G<sub>1</sub>, growth factor signaling leads to cyclin D expression, activation of the CDK4/cyclin D complexes, inactivation of RB by phosphorylation, and thus release of E2F. This is a fundamental mechanism of cell cycle control. Almost all cancers will have disabling mutation of either *RB* or genes that affect RB function, like cyclin D, CDK4, or *p16*. Oncogenic DNA viruses, like HPV, encode proteins (e.g., E7) that bind to RB and inactivate it, rendering it nonfunctional.

### ***p53 Gene: Guardian of the Genome***

The *p53* tumor suppressor gene is one of the most commonly mutated genes in human cancers. It acts through three interlocking mechanisms: activation of temporary cell cycle arrest (termed quiescence), induction of permanent cell cycle arrest (termed senescence), or triggering of programmed cell death (termed apoptosis). Fundamentally, *p53* acts as a sensor of stress, directing the stressed cells toward an appropriate response. A variety of stresses can trigger *p53*, including anoxia, inappropriate oncogene expression (e.g., *MYC* or *RAS*), and damage to the integrity of the genome. In response to DNA damage, *p53* plays a central role in maintaining the integrity of the genome, as will be discussed below.

In nonstressed, healthy cells, *p53* has a short half-life (20 minutes) because of its association with MDM2, which targets it for destruction. When the cell is stressed, for example by an assault on its DNA, *p53* undergoes post-translational modification, is released from MDM2, and increases its half-life. During the process of being unshackled from MDM2, *p53* acts as a transcription factor. Dozens of genes whose transcription is triggered by *p53* have been found. They can be grouped into three categories: those that cause cell cycle arrest and those that cause apoptosis. If DNA damage can be repaired during the cell cycle arrest, the cell can return to its normal state; if the repair fails, *p53* induces apoptosis or senescence. These actions are discussed in more detail below.

The manner in which *p53* senses DNA damage and determines the adequacy of DNA repair are not fully understood. Two initiators of the DNA-damage pathway are two related protein kinases: *ataxia-telangiectasia mutated* (*ATM*) and *ataxia-telangiectasia mutated related* (*ATR*). As the name implies, the *ATM* gene was originally identified as the gene mutated in ataxia-telangiectasia. Patients with this disease, which is characterized by an inability to repair certain kinds of DNA damage, have an increased incidence of cancer. The types of damage sensed by *ATM* and *ATR* are different, but their functions are similar. Once triggered, both *ATM* and *ATR* phosphorylate a variety of targets, including *p53*. Phosphorylation of these two targets leads to a pause in the cell cycle and stimulation of DNA repair pathways responsible for maintaining genomic integrity.

*p53-mediated cell cycle arrest may be considered the primordial response to DNA damage (Fig. 6.10). This response is caused mainly by p53-dependent transcription of the CDKI CDKN1A (p21). The CDKN1A gene, a member of the CDK inhibitor family, forms a complex with CDK2 and prevents phosphorylation of RB essential for cells to enter G<sub>1</sub> phase. Such a pause in the cell cycle allows time for DNA repair. If the damage is irreparable, p53 induces apoptosis or senescence.*



gives the cells "breathing time" to repair DNA damage. p53 also helps the process by inducing cell arrest and DNA damage), that help in DNA repair. p53 can stimulate DNA repair pathways by transcribing various genes. If DNA damage is repaired successfully, p53 up-regulates transcription of MDM2, leading to cell cycle block. If the damage cannot be repaired, the cell may enter p53-induced senescence or undergo apoptosis.

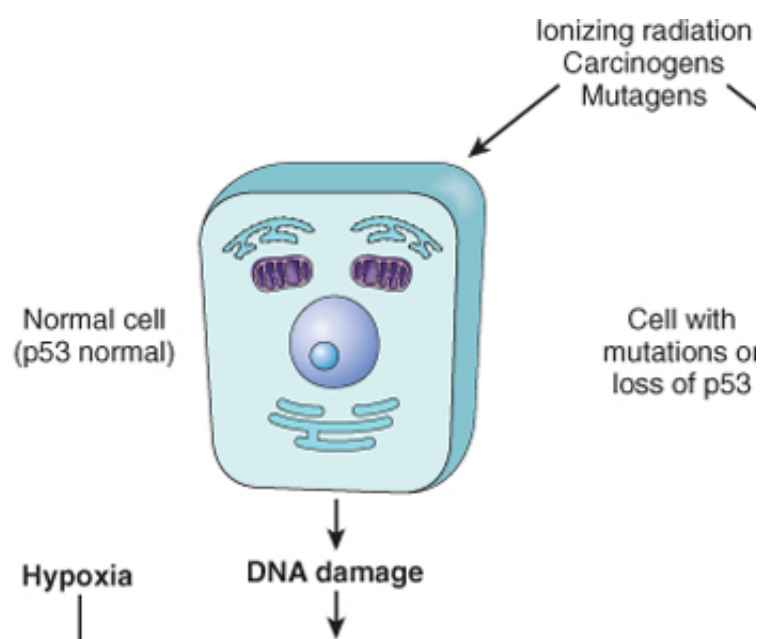
*p53-induced senescence is a permanent cell cycle arrest* characterized by specific changes in morphology and gene expression that differentiate it from quiescence or reversible cell cycle arrest. Senescence requires activation of p53-dependent transcriptional mediators, such as the CDKIs. Such cell cycle arrest is generally irreversible, although it may require additional mechanisms of senescence are unclear but seem to involve global chromatin changes, which drive the expression of senescence-associated genes.

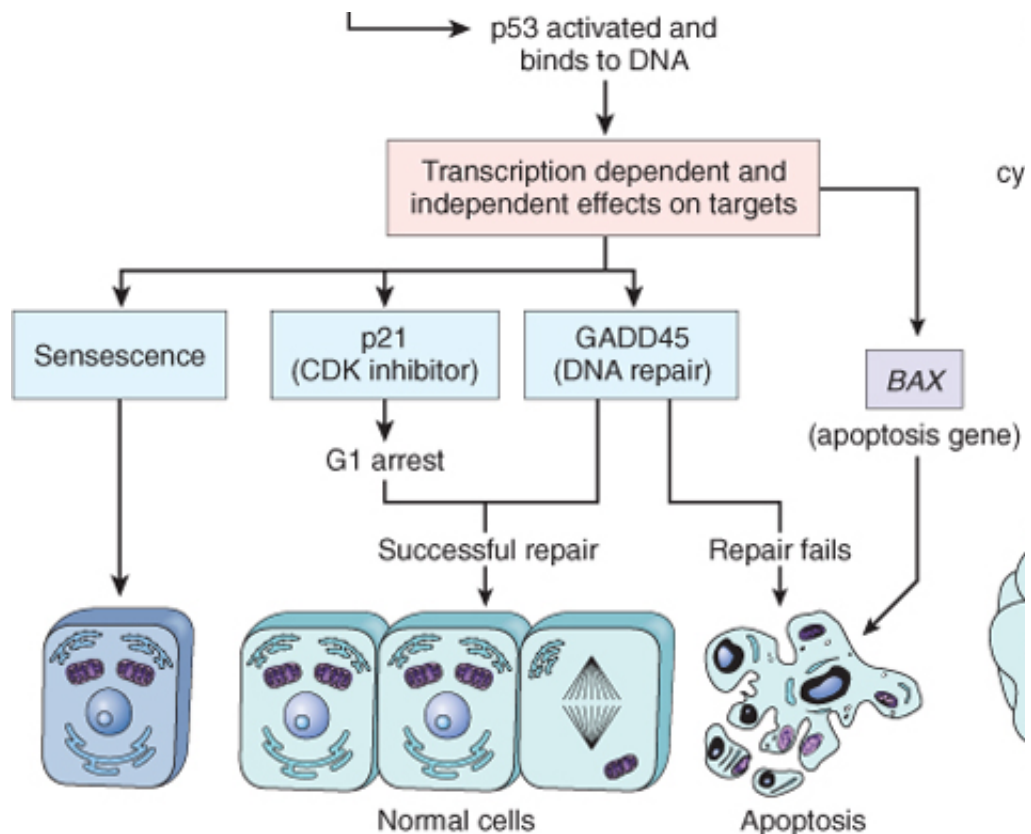
p53-induced apoptosis of cells with irreversible DNA damage is the ultimate protective mechanism mediated by several pro-apoptotic genes such as *BAX* and *PUMA* (described later).

To summarize, p53 senses DNA damage and assists in DNA repair by causing G<sub>1</sub> arrest and inducing apoptosis. If damaged DNA that cannot be repaired is detected by p53, the cell is directed to either enter senescence or undergo apoptosis. p53 has been rightfully called a "guardian of the genome." With homozygous loss of p53, mutations become fixed in dividing cells, and the cell turns onto a one-way street leading to malignancy.

Confirming the importance of p53 in controlling carcinogenesis, more than 70% of human cancers remaining malignant neoplasms have defects in genes up-stream or down-stream of p53. Homozygous loss of p53 occurs in virtually every type of cancer, including carcinomas of the lung, colon, and breast—the three leading causes of cancer death. Inactivating mutations affecting both p53 alleles are acquired in somatic cells. Less common is the inherited loss of one p53 allele; this disease is called the *Li-Fraumeni syndrome*. As with the *RB* gene, inheritance of one mutant p53 allele predisposes to develop malignant tumors because only one additional hit is needed to inactivate the second, normal p53 allele. Patients with *Li-Fraumeni syndrome* have a 25-fold greater chance of developing a malignant tumor by age 50 compared to patients who inherit a mutant *RB* allele, the spectrum of tumors that develop in patients is varied; the most common types of tumors are sarcomas, breast cancer, leukemia, brain tumors, and adrenocortical carcinoma. Compared with sporadic tumors, patients with *Li-Fraumeni syndrome* develop tumors at a younger age.

As with RB protein, normal p53 also can be rendered nonfunctional by certain DNA viruses. Proteins from hepatitis B virus (HBV), and possibly Epstein-Barr virus (EBV) can bind to normal p53 and nullify its function. These viruses can subvert two of the best-understood tumor suppressor genes, *RB* and *p53*.





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 Figure 6-22 The role of *p53* in maintaining the integrity of the genome. Activation of normal *p53* by DNA-damaging agents in the  $G_1$  phase of the cell cycle leads to transcriptional up-regulation of the cyclin-dependent kinase inhibitor *CDKN1A* (*p21*). This results in  $G_1$  arrest and induction of DNA repair. If DNA repair is successful, the cell cycle proceeds; if DNA repair fails, *p53* triggers either apoptosis or senescence. DNA damage does not induce cell cycle arrest or DNA repair, and genetically damaged cells proliferate, giving

## SUMMARY

### *p53* Gene: Guardian of the Genome

*p53* is the central monitor of stress in the cell and can be activated by anoxia, oxidative stress, or DNA damage. Activated *p53* controls the expression and activity of genes involved in cell cycle arrest, DNA repair, cellular senescence, and apoptosis. DNA damage is sensed by the *p53* protein, which is then phosphorylated and activated. Activated *p53* drives transcription of *CDKN1A* (*p21*) and *GADD45*, leading to cell cycle arrest and DNA repair. If DNA damage cannot be repaired, *p53* induces cellular senescence or apoptosis. Of human tumors, 70% have homozygous loss of *p53*. Patients with Li-Fraumeni syndrome inherit one defective copy in the germ line and lose the second copy. Individuals develop a variety of tumors. As with RB, *p53* can be inactivated or encoded by oncogenic DNA viruses like HPV, and possibly EBV and HBV.

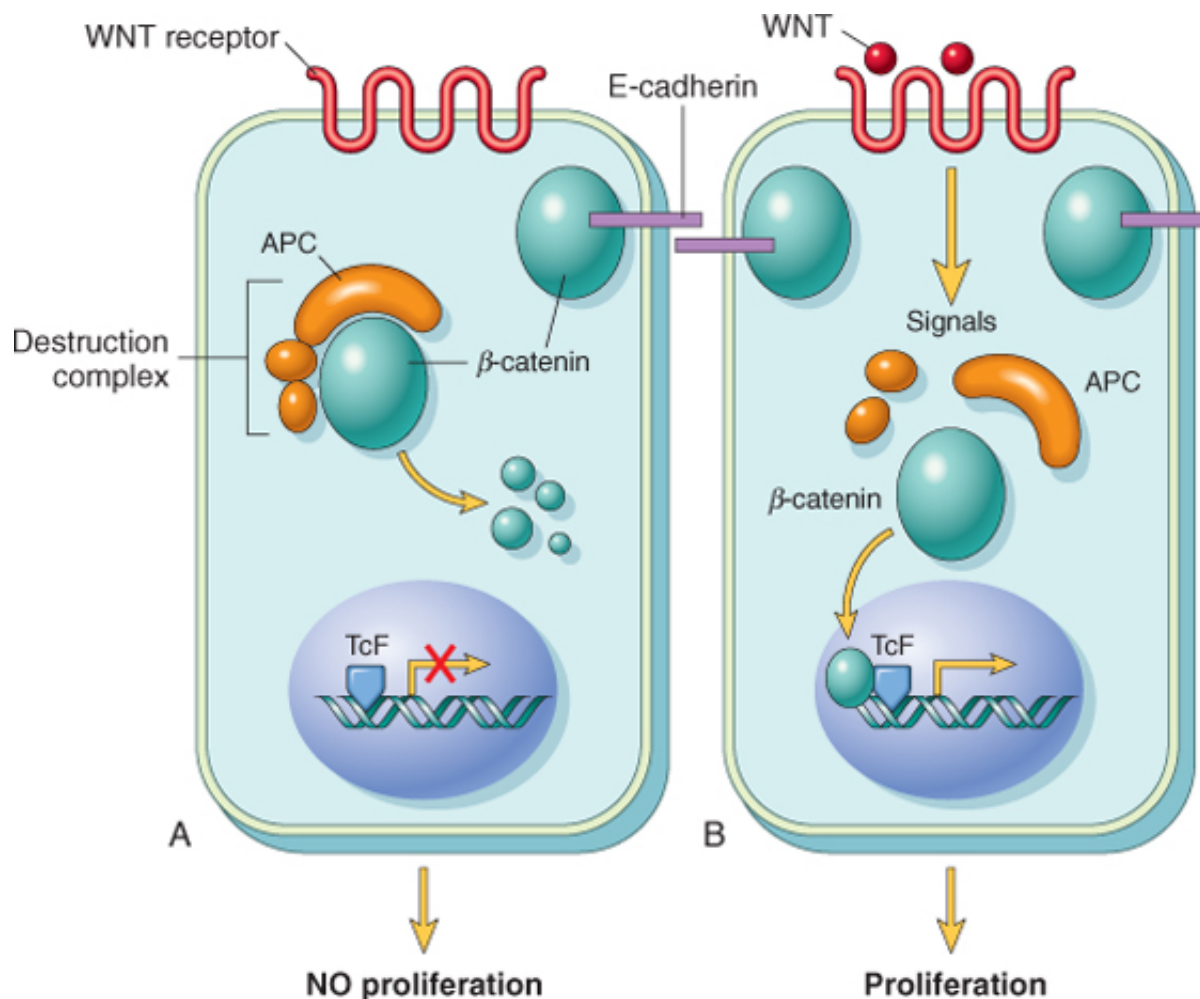
### Transforming Growth Factor- $\beta$ Pathway

Although much is known about the circuitry that applies brakes to the cell cycle, the molecules that are less well characterized. Best known is TGF- $\beta$ , a member of a family of dimeric growth factors, cytokines, and activins. In most normal epithelial, endothelial, and hematopoietic cells, TGF- $\beta$  is a potent inhibitor of cellular processes by binding to a complex composed of TGF- $\beta$  receptors I and II. Dimerization of these receptors initiates a cascade of events that result in the transcriptional activation of CDKIs with growth-suppressing activity.

promoting genes such as *c-MYC*, *CDK2*, *CDK4*, and cyclins A and E.

In many forms of cancer, the growth-inhibiting effects of TGF- $\beta$  pathways are impaired by mutations. Mutations may affect the type II TGF- $\beta$  receptor or SMAD molecules that serve to transduce anti-proliferative signals to the nucleus. Mutations affecting the type II receptor are seen in cancers of the colon, stomach, and esophagus. SMAD4, one of 10 proteins involved in TGF- $\beta$  signaling, is common in pancreatic cancers. *In 100% of colon cancers, at least one component of the TGF- $\beta$  pathway is mutated.*

### **Adenomatous Polyposis Coli- $\beta$ -Catenin Pathway**



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Figure 6-23 A-C, The role of APC in regulating the stability and function of  $\beta$ -catenin. APC and  $\beta$ -catenin are components of the destruction complex. In cells (not exposed to WNT),  $\beta$ -catenin forms a macromolecular complex containing the APC protein. This complex targets  $\beta$ -catenin for degradation, and intracellular levels of  $\beta$ -catenin are low. When cells are stimulated by secreted WNT molecules, the destruction complex is inhibited, and cytoplasmic levels of  $\beta$ -catenin increase.  $\beta$ -catenin translocates to the nucleus, where it binds to TcF, a transcription factor that activates the cell cycle. When APC is mutated or absent, the destruction of  $\beta$ -catenin cannot occur.  $\beta$ -catenin translocates to the nucleus, and cells behave as if they are under constant stimulation by the WNT pathway.

In the rare hereditary disease called adenomatous polyposis coli (APC), patients develop numerous polyps in the colon. These patients have a very high incidence of transformation into colonic cancers. These patients consistently have a mutation in the APC gene (named for the disease). The APC gene exerts antiproliferative effects in an unusual manner. Its dominant function is to regulate the intracellular levels of  $\beta$ -catenin, a protein with many functions.  $\beta$ -catenin has a cytoplasmic portion of E-cadherin, a cell surface protein that mediates intercellular interactions; or nucleus and activate cell proliferation. Here the focus is on the latter function of this protein.  $\beta$ -catenin

called WNT signaling pathway that regulates cell proliferation (illustrated in Fig. 6-23). WNT is a secreted protein that binds to its receptor and transmitting signals that prevent the degradation of  $\beta$ -catenin. In quiescent cells, which are not exposed to WNT, cytoplasmic  $\beta$ -catenin is degraded by a destruction complex (see Fig. 6-23A). With loss of APC (in malignant cells),  $\beta$ -catenin degradation is prevented, and it is inappropriately activated in the absence of WNT (see Fig. 6-23C). This leads to transcription of *c-myc* and *MYC*.

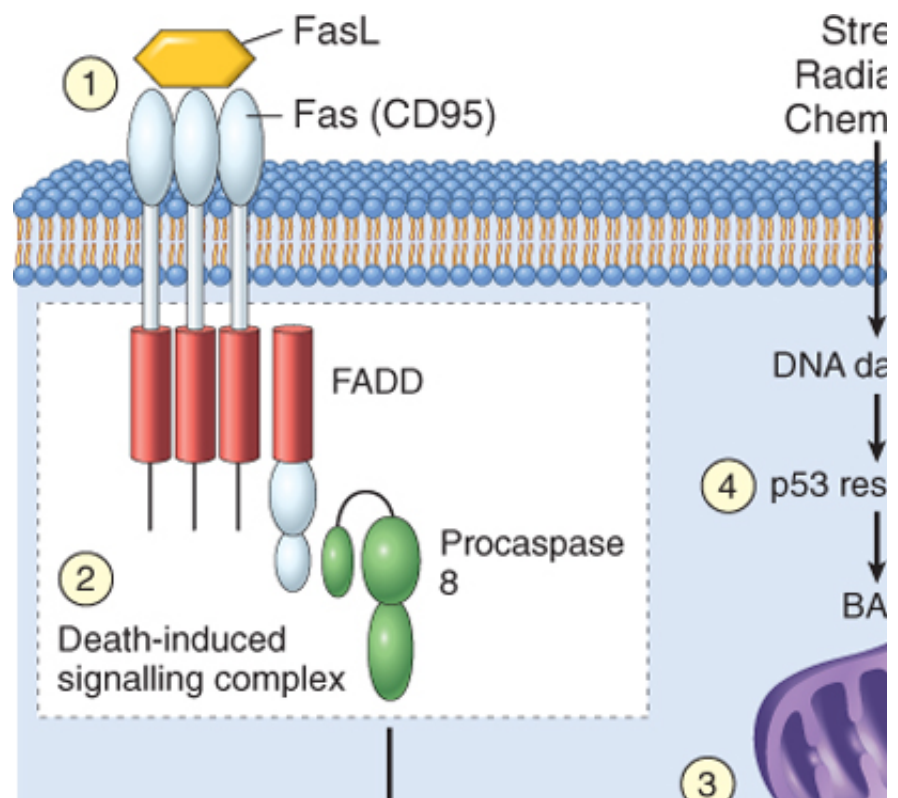
*APC* behaves as a typical tumor suppressor gene. Individuals born with one mutant allele develop polyps in the colon during their teens or 20s, which show loss of the other *APC* allele. Almost invariably, malignant transformation upon accumulation of other mutations in the cells within the polyp, as described in 70% to 80% of sporadic colon cancers. Colonic cancers that have normal *APC* genes show active  $\beta$ -catenin, which is refractory to the degrading action of APC.

## SUMMARY

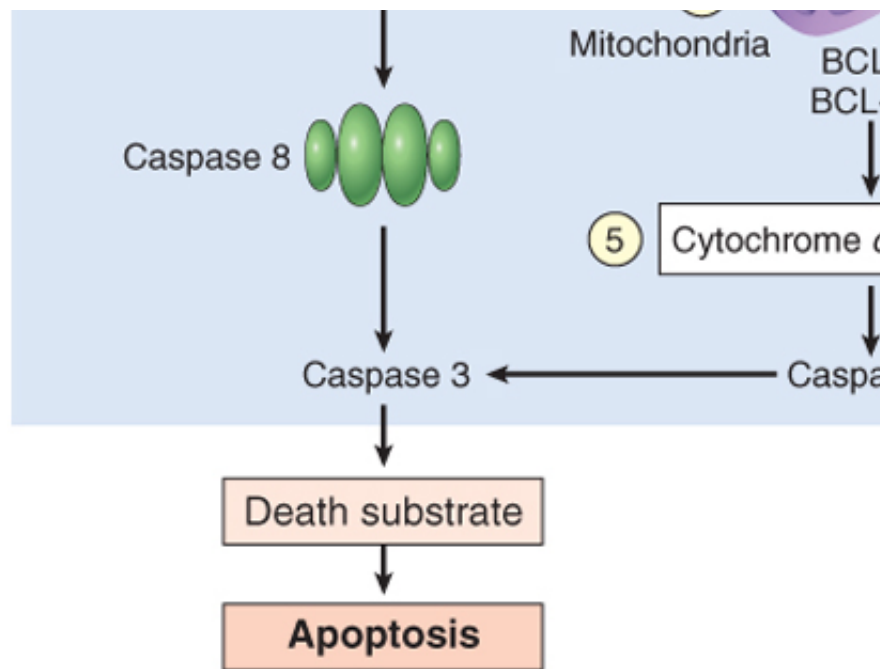
### Transforming Growth Factor- $\beta$ and Adenomatous Polyposis Coli- $\beta$ -Catenin Pathway

TGF- $\beta$  inhibits proliferation of many cell types by activation of growth-inhibitory genes and suppression of growth-promoting genes like *MYC* and cyclins. TGF- $\beta$  functions as a tumor suppressor in many tumors by mutations in its receptors (colon, stomach, endometrium) or by mutations in *SMAD* genes that transduce TGF- $\beta$  signaling (pancreas). *APC* gene exerts its function by regulating the destruction of the cytoplasmic protein  $\beta$ -catenin. With a loss of APC,  $\beta$ -catenin is not destroyed and it translocates to the nucleus, where it acts as a growth-promoting factor. In familial adenomatous polyposis syndrome inheritance of a germ-line mutant *APC* gene causes the development of hundreds of colonic polyps at a young age. A polyp eventually evolves into a colonic cancer with loss of heterozygosity at the *APC* locus. The loss of one allele of the *APC* gene is seen in approximately 70% of sporadic colon cancers.

## Evasion of Apoptosis







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Figure 6-24 Simplified schema of CD95 receptor-induced and DNA damage-triggered pathways of apoptosis and death. (1) Reduced CD95 level. (2) Inactivation of death-induced signaling complex by FLICE protein. (3) Reduced result of up-regulation of BCL2. (4) Reduced levels of pro-apoptotic BAX resulting from loss of p53. (5) Loss of AP.

Accumulation of neoplastic cells may result not only from activation of growth-promoting oncogenes, but also from mutations in the genes that regulate apoptosis. A large number of tumor suppressor genes have been identified. Before we can understand how tumor cells evade apoptosis, it is essential to review the basic principles of apoptosis. As discussed in Chapter 1, there are two distinct programs that activate apoptosis, the extrinsic pathway (initiated by CD95 receptor) and the intrinsic pathway (initiated by DNA damage and other factors). The extrinsic pathway is initiated when CD95 is activated, leading to trimerization of the receptor and thus its cytoplasmic *death domains*, which attract the intracellular proteins FADD and caspase 8. Caspase 8 is activated by cleavage, generating active caspase 8. Caspase 8 then activates downstream caspases such as caspase 3, a type of executioner caspase. Caspase 3 cleaves various substrates to cause cell death. The intrinsic pathway of apoptosis is triggered by a variety of factors, including DNA damage, survival factors, stress, and injury. Activation of this pathway leads to permeabilization of mitochondrial membranes and release of molecules, such as cytochrome c, that initiate apoptosis. The integrity of the mitochondrial membrane is regulated by apoptotic and anti-apoptotic members of the BCL2 family of proteins. The pro-apoptotic proteins, including BAX and BAK, directly promote mitochondrial permeabilization. Their action is inhibited by the anti-apoptotic proteins BCL2 and BCL-XL. A third set of proteins (so-called BH3-only proteins) including BAD, BID, and BCL-2L1, act as pro-apoptotic members of the BCL2 family. The BH3-only proteins promote apoptosis by neutralizing the anti-apoptotic effect of BCL2 and BCL-XL. When the sum total of all BH3 proteins expressed "overwhelms" the anti-apoptotic barrier, BAX and BAK are activated and form pores in the mitochondrial membrane. Cytochrome c is released and binds to APAF-1, activating caspase 9. Like caspase 8 of the extrinsic pathway, caspase 9 can cleave and activate caspase 3. Because of the pro-apoptotic effect of BH3 only proteins, efforts are underway to develop of BH3 inhibitors.

Within this framework, it is possible to illustrate the multiple sites at which apoptosis is frustrated by tumor cells. From the surface, reduced levels of CD95 may render the tumor cells less susceptible to apoptosis. Tumor cells may have high levels of FLIP, a protein that can bind death-inducing signaling complex and prevent activation of caspase 8. Perhaps the best established is the role of BCL2 in protecting tumor cells from apoptosis. As discussed in Chapter 12, lymphomas of the follicular type (Chapter 12) carry a characteristic t(14;18) (q32;q21) translocation. The immunoglobulin heavy-chain genes are found, is also involved in the pathogenesis of Burkitt lymphoma. The transcriptionally active locus with BCL2 (located at 18q21) causes overexpression of the BCL2 protein.

BCL2/BCL-XL buffer, protecting lymphocytes from apoptosis and allowing them to survive for long accumulation of B lymphocytes, resulting in lymphadenopathy and marrow infiltration. Because B cells die in large part from reduced cell death rather than explosive cell proliferation, they tend to be indolent lymphomas.

As mentioned before, *p53 is an important pro-apoptotic gene that induces apoptosis in cells that are damaged*. The actions of *p53* are mediated in part by transcriptional activation of *BAX*, but there are other connections to the apoptotic machinery.

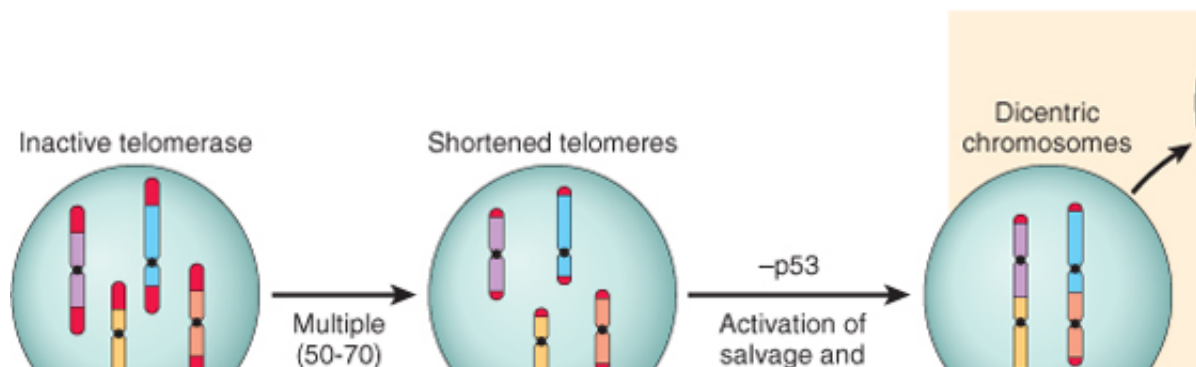
## SUMMARY

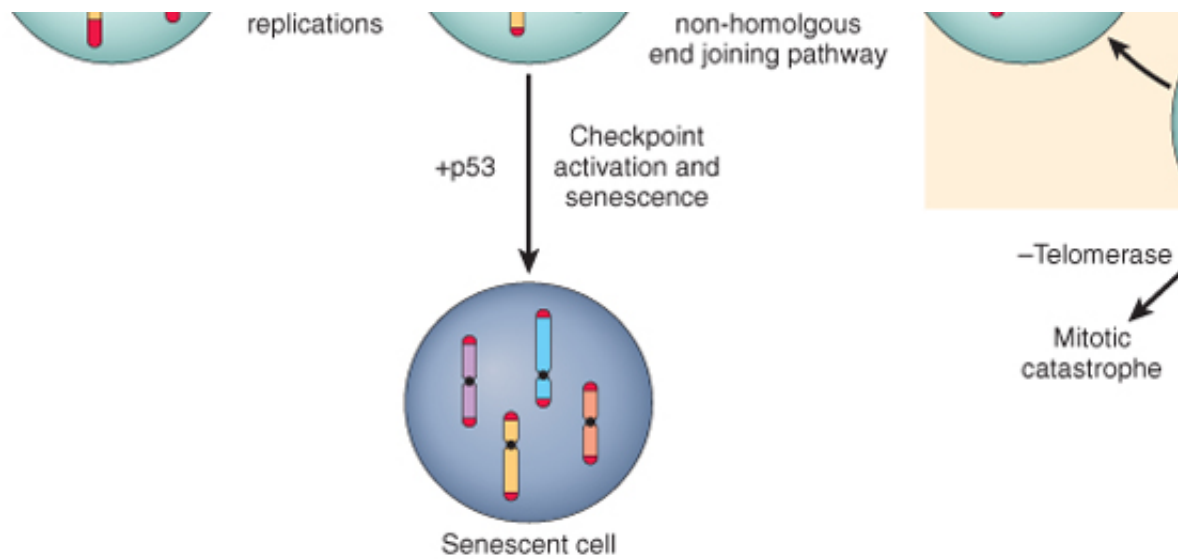
### Evasion of Apoptosis

Apoptosis can be initiated through the extrinsic or intrinsic pathways. Both pathways lead to the activation of a proteolytic cascade of caspases that destroys the cell. Mitochondrial outer membrane permeabilization is regulated by the balance between pro-apoptotic (e.g., BAX, Bak) and anti-apoptotic molecules (BCL2, BCL-XL). BH-3-only molecules activate apoptosis by tipping the balance in favor of the pro-apoptotic molecules. In 85% of follicular B-cell lymphomas the *BCL2* gene is activated by the t(14;18) translocation.

### Limitless Replicative Potential

As was discussed in the section on cellular aging (Chapter 1), most normal human cells have a capacity to divide, but as they age, the cells lose the capacity to divide and enter senescence. This phenomenon has been ascribed to the shortening of the ends of chromosomes. Indeed, short telomeres seem to be recognized by the DNA repair machinery, and this leads to cell cycle arrest mediated by *p53* and *RB*. Cells in which the checkpoints are disabled, the nonhomologous end-joining pathway is activated as a last-ditch effort to save the cell, joining the broken ends. This inappropriately activated repair system results in dicentric chromosomes that are pulled apart during the next cell division, leading to DNA breaks. The resulting genomic instability from the repeated bridge-fusion-breakage cycle is a catastrophe, characterized by massive cell death. *It follows that for tumors to grow indefinitely, as they do, they must also develop ways to avoid both cellular senescence and mitotic catastrophe.* Tumor cells must also develop ways to avoid both cellular senescence and mitotic catastrophe. Tumor cells manage to reactivate telomerase, the bridge-fusion-breakage cycles cease and the cell is able to divide. In the absence of genomic instability that precedes telomerase activation, numerous mutations could accumulate over time. Passage through a period of genomic instability probably explains the complex karyotypes of many human carcinomas. Telomerase, active in normal stem cells, is normally absent from, or at very low levels in, most somatic cells. Telomere maintenance is seen in virtually all types of cancers. In 85% to 95% of cancers, this is due to reactivation of telomerase. A few tumors use other mechanisms, termed alternative lengthening of telomeres, which involve homologous recombination. Interestingly, in the progression from colonic adenoma to colonic adenocarcinoma, there is a period of genomic instability with low telomerase expression, whereas malignant lesions had complex karyotypes and high telomerase activity, consistent with a model of telomere-driven tumorigenesis in human cancer. Several other mechanisms are discussed later.





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Figure 6-25 Schematic illustration of the sequence of events in the development of limitless replicative potential. R telomerase, leads to shortened telomeres. In the presence of competent checkpoints, cells undergo arrest and end checkpoints, DNA repair pathways are inappropriately activated, leading to the formation of dicentric chromosomes pulled apart, generating random double-stranded breaks, which then activate DNA repair pathways, leading to the the formation, again, of dicentric chromosomes. Cells undergo numerous rounds of this bridge-fusion-breakage instability and numerous mutations. If cells fail to re-express telomerase, they eventually undergo mitotic catastrophe the cells to escape the bridge-fusion-breakage cycle, thus promoting their survival a

## SUMMARY

### Limitless Replicative Potential

In normal cells, which lack expression of telomerase, the shortened telomere division eventually activate cell cycle checkpoints, leading to senescence after a number of divisions a cell may undergo. In cells that have disabled checkpoints, they are inappropriately activated by shortened telomeres, leading to massive chromosome breakage and mitotic crisis. Tumor cells reactivate telomerase, thus staving off mitotic catastrophe and achieving immortality.

## Development of Sustained Angiogenesis

Even with all the genetic abnormalities discussed above, tumors cannot enlarge beyond 1 to 2 mm and are not fully vascularized. Like normal tissues, tumors require delivery of oxygen and nutrients and removal of waste. The 1 mm zone represents the maximal distance across which oxygen, nutrients, and waste can diffuse. Beyond this zone, hypoxia stimulates neo-angiogenesis, during which new vessels sprout from previously existing capillaries, which endothelial cells are recruited from the bone marrow (Chapter 3). Tumor vasculature is abnormal, dilated, and has a haphazard pattern of connection. Neovascularization has a dual effect on tumor growth: it provides nutrients and oxygen, and newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting insulin-like growth factors, PDGF, and granulocyte-macrophage colony-stimulating factor. Angiogenesis promotes tumor growth but also for access to the vasculature and hence for metastasis. *Angiogenesis is the hallmark of malignancy.*

How do growing tumors develop a blood supply? The emerging paradigm is that tumor angiogenesis is regulated by angiogenic factors and factors that inhibit angiogenesis. Early in their growth, most human tumors remain small or in situ for years until the angiogenic switch terminates this stage of quiescence. The angiogenic switch involves increased production of angiogenic factors and/or loss of angiogenesis inhibitors. Angiogenic factors are produced directly by the tumor cells themselves or by inflammatory cells (e.g., macrophages) or by

tumors. The angiogenic switch is controlled by several physiologic stimuli, such as hypoxia. Release of a variety of pro-angiogenic cytokines, such as vascular endothelial growth factor (VEGF), through HIF1 $\alpha$  (HIF1 $\alpha$ ), an oxygen-sensitive transcription factor. HIF1 $\alpha$  is continuously produced, but in normal cells, a protein (VHL) binds to HIF1 $\alpha$ , leading to ubiquitination and destruction of HIF1 $\alpha$ . In hypoxic conditions, the lack of oxygen prevents HIF1 $\alpha$  recognition by VHL, and it is not destroyed. HIF1 $\alpha$  promotes transcription of its target genes, such as VEGF. Because of these activities, VHL acts as a tumor suppressor gene. Mutations of the *VHL* gene are associated with hereditary renal cell cancers, pheochromocytoma, von Hippel-Lindau disease, retinal angiomas, and renal cysts (*VHL syndrome*). Both pro- and anti-angiogenic factors are frequently mutated in cancer. For example, in normal cells, *p53* can stimulate expression of anti-angiogenic factors like thrombospondin-1, and repress expression of pro-angiogenic molecules, such as VEGF. Thus, loss of *p53* promotes the cell cycle checkpoints listed above, but also provides a more permissive environment for angiogenesis, which is also influenced by signals from the RAS-MAP kinase pathway, and mutations of *RAS* or *MYC* up-

regulate angiogenesis. Proteases, either elaborated by the tumor cells directly or from stromal cells in response to the tumor, balance between angiogenic and anti-angiogenic factors. Many proteases can release the angiogenic matrix (ECM); conversely, three potent angiogenesis inhibitors—angiostatin, endostatin, and vasculostatin—block cleavage of plasminogen, collagen, and transthyretin, respectively. Because of the crucial role of proteases in angiogenesis, interest is focused on anti-angiogenesis therapy. Indeed, anti-VEGF antibody is now approved for cancer treatment.

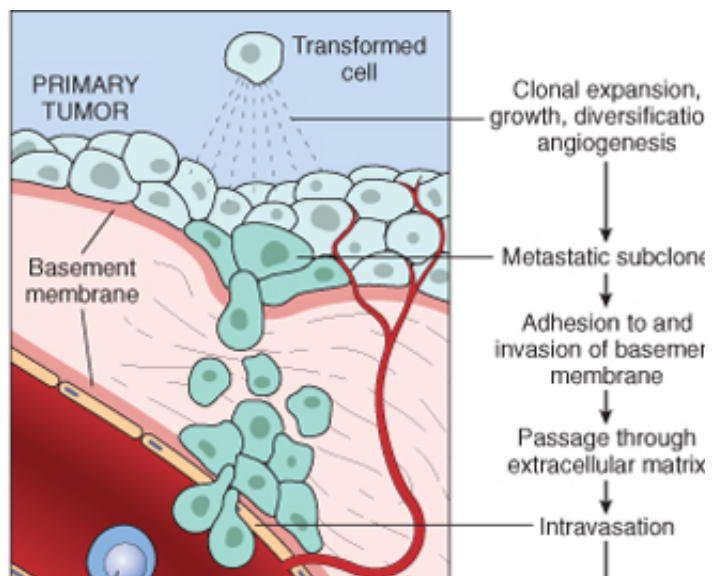
## SUMMARY

### Development of Sustained Angiogenesis

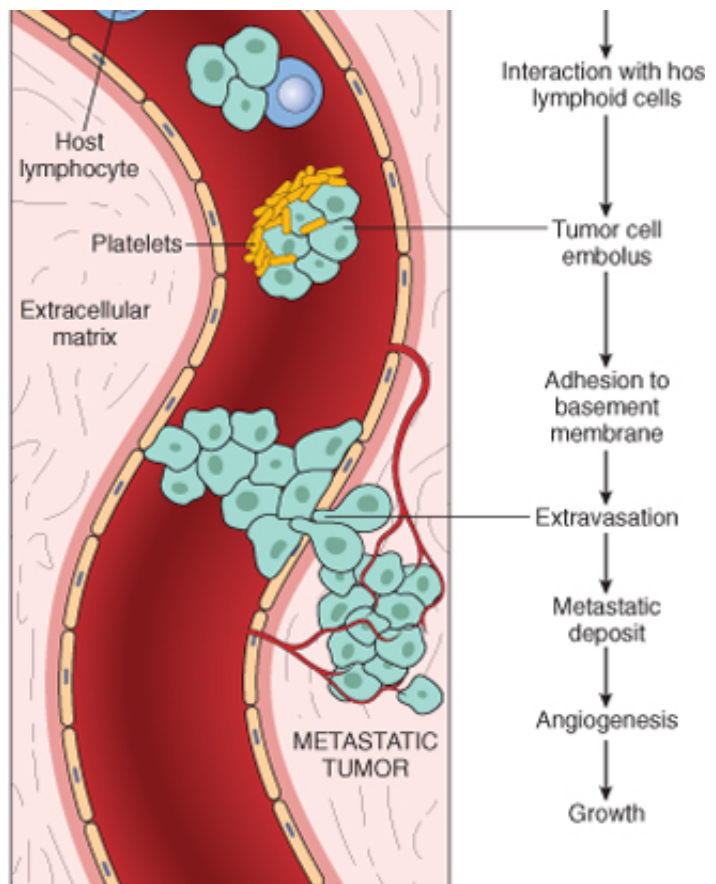
Vascularization of tumors is essential for their growth and is controlled by the balance between angiogenic and anti-angiogenic factors that are produced by tumor and stromal cells. Angiogenesis occurs through the actions of HIF1 $\alpha$ . Because of its ability to degrade the basement membrane, VHL acts as a tumor suppressor gene. Inheritance of germ-line mutations of *VHL* causes VHL syndrome, characterized by the development of a variety of tumors. Tumor cells can also regulate angiogenesis; for example, *p53* induces synthesis of the anti-angiogenic factor thrombospondin-1.

### Ability to Invade and Metastasize

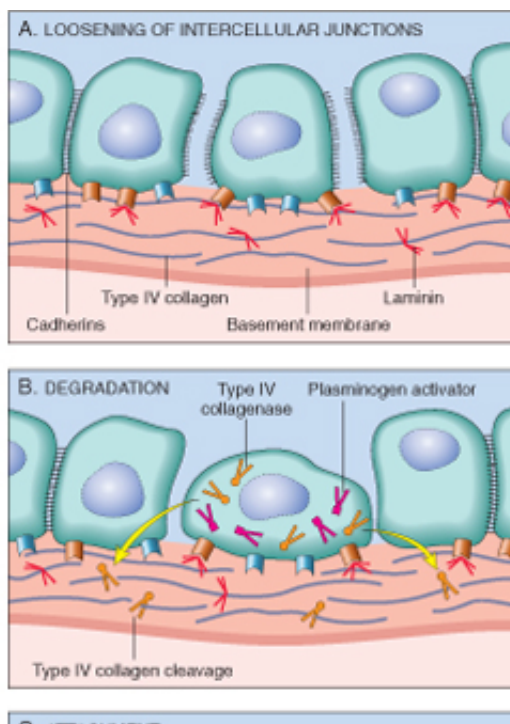
The spread of tumors is a complex process involving a series of sequential steps, diagrammed in Figure 1. These steps may be interrupted at any stage by either host-related or tumor-related factors. For the purpose of this discussion, the cascade can be subdivided into two phases: invasion of ECM and vascular dissemination, and homing to distant sites.

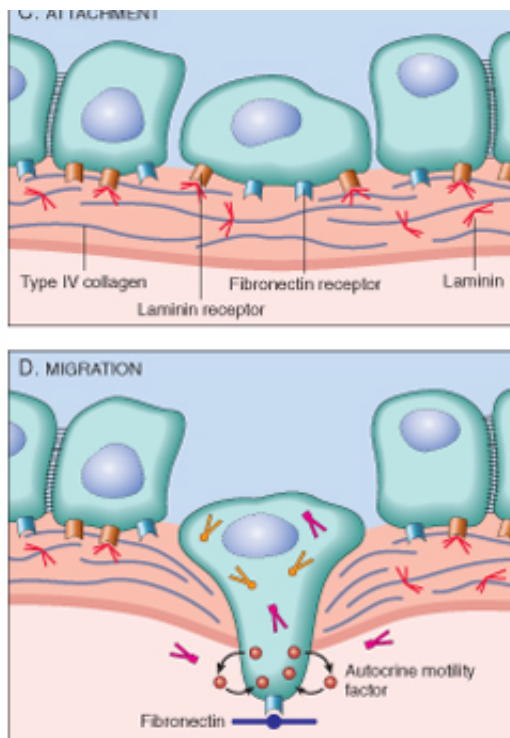






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 Figure 6-26 The metastatic cascade. Schematic illustration of the sequential steps involved in the





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 Figure 6-27 **A-D**, Schematic illustration of the sequence of events in the invasion of epithelial basement membrane other because of reduced adhesiveness, then secrete proteolytic enzymes, degrading the basement membrane. I and tumor cell migration follow.

### ***Invasion of Extracellular Matrix (ECM)***

As is well known, human tissues are organized into a series of compartments separated from each other by cell membranes and interstitial connective tissue. Though organized differently, each of these compartments contains glycoproteins, and proteoglycans. A review of Figure 6-26 reveals that tumor cells must interact with the extracellular matrix (ECM) to undergo a metastatic cascade. A carcinoma first must breach the underlying basement membrane, then travel through the interstitial matrix, and ultimately gain access to the circulation by penetrating the vascular basement membrane. This cycle of invasion and metastasis. Thus, to metastasize, a tumor cell must cross several different barriers. Invasion of the ECM is an active process that requires for

1. Detachment of tumor cells from each other
2. Degradation of ECM
3. Attachment to novel ECM components
4. Migration of tumor cells

The first step in the metastatic cascade is a *loosening* of tumor cells. As mentioned earlier, E-cadherin cytoplasmic portions bind to  $\beta$ -catenin (see Fig. 6-23). Adjacent E-cadherin molecules keep the cells together. Earlier, E-cadherin can transmit antigrowth signals by sequestering  $\beta$ -catenin. *E-cadherin function is either by mutational inactivation of E-cadherin genes, by activation of  $\beta$ -catenin genes, or by inappropriate TWIST transcription factors, which suppress E-cadherin expression.*

The second step in invasion is local *degradation of the basement membrane and interstitial connective tissue*. Tumor cells secrete proteolytic enzymes themselves or induce stromal cells (e.g., fibroblasts and inflammatory cells) to secrete different families of proteases, such as matrix metalloproteinases (MMPs), cathepsin D, and urokinase-type plasminogen activator (uPA) implicated in tumor cell invasion. MMPs regulate tumor invasion not only by remodeling insoluble ECM and interstitial matrix but also by releasing ECM-sequestered growth factors. Indeed, cleavage products of

have chemotactic, angiogenic, and growth-promoting effects. For example, MMP-9 is a gelatinase that degrades basement membrane and also stimulates release of VEGF from ECM-sequestered factors. Primary tumors of the breast, colon, and stomach show little type IV collagenase activity, whereas their malignant counterparts do. Concurrently, the levels of metalloproteinase inhibitors are reduced so that the balance is tilted greatly in favor of MMPs. Overexpression of MMPs and other proteases have been reported for many tumors. Because of this, it has been made to use protease inhibitors as therapeutic agents.

The third step in invasion involves *changes in attachment of tumor cells to ECM proteins*. Normal cells are attached to basement membrane laminin and collagens that are polarized at their basal surface; in a resting, differentiated state. Loss of adhesion in normal cells leads to induction of apoptosis, and tumor cells are resistant to this form of cell death. Additionally, the matrix itself is modified in ways that promote invasion. Cleavage of the basement membrane proteins collagen IV and laminin by MMP-2 or MMP-9 gene products in tumor cells and stimulate migration.

*Locomotion* is the final step of invasion, propelling tumor cells through the degraded basement membrane by proteolysis. Migration is a complex, multistep process that involves many families of receptors and integrins that impinge on the actin cytoskeleton. Such movement seems to be potentiated and directed by tumor cell autocrine motility factors. In addition, cleavage products of matrix components (e.g., collagen, laminin, and insulin-like growth factors I and II) have chemotactic activity for tumor cells. Stromal cells also produce factors such as hepatocyte growth factor/scatter factor (HGF/SCF), which bind to receptors on tumor cells. These factors are elevated at the advancing edges of the highly invasive brain tumor glioblastoma multiforme, supporting further invasion.

It has become clear in recent years, however, that the ECM and stromal cells surrounding tumor cells are not a barrier for tumor cells to traverse but rather represent a variable environment in which reciprocal interactions between tumor cells and stromal cells may either promote or prevent tumorigenesis and/or tumor progression. Stromal cells that include adaptive immune cells (discussed later), as well as fibroblasts. A variety of studies have demonstrated that stromal cells exhibit altered expression of genes that encode ECM molecules, proteases, protease inhibitors, and growth factors. Cells live in a complex and ever-changing milieu composed of ECM, growth factors, fibroblasts, and immune cells, among all the components. The most successful tumors may be those that can co-opt and adapt to the stromal environment.

### ***Vascular Dissemination and Homing of Tumor Cells***

When in the circulation, tumor cells are vulnerable to destruction by host immune cells (discussed later). Tumor cells form emboli by aggregating and adhering to circulating leukocytes, particularly platelets; aggregate formation provides some protection from the antitumor host effector cells. Most tumor cells, however, circulate as single cells. Tumor embolism or tumor emboli involves adhesion to the vascular endothelium, followed by egress through the basement membrane into the parenchyma by mechanisms similar to those involved in invasion.

The site of extravasation and the organ distribution of metastases generally can be predicted by the pattern of vascular or lymphatic drainage. Many tumors metastasize to the organ that represents the first capillary bed encountered in the circulation. However, in many cases the natural pathways of drainage do not readily explain the pattern of metastasis. For example, out earlier, some tumors (e.g., lung cancers) tend to involve the adrenals with some regularity but not the liver. Such organ tropism may be related to the expression of adhesion molecules by tumor cells whose receptors bind to molecules on the endothelium of target organs. Another mechanism of site-specific homing involves chemokines. Chemokines participate in directed movement (chemotaxis) of leukocytes, and it seems that tumor cells also home in on specific tissues. Human breast cancer cells express high levels of the chemokine receptors CXCR4 and CXCR2. These receptors (i.e., chemokines CXCL12 and CCL21) are highly expressed only in those organs that are permissive for tumor growth. On the basis of this observation, it is speculated that blockade of chemokine receptors may limit tumor growth. Tumor cells are dependent on a receptive stroma for growth. Thus, tumors may fail to metastasize to certain organs if the stroma is nonpermissive for growth. Despite the foregoing considerations, the precise localization of metastases is unpredictable in any form of cancer. Evidently many tumors have not read the relevant chapters of the pathology text.

### ***Molecular Genetics of Metastasis***

A long-held theory of tumor progression suggests that, as tumors grow, individual cells randomly acquire mutations that confer growth advantages. These mutations are passed on to daughter cells, and over time, a population of cells with a high degree of genetic heterogeneity is established. This theory is supported by the observation that tumors of the same histologic type and origin often have different patterns of metastasis. This suggests that the pattern of metastasis is determined by the genetic makeup of the tumor cells at the time of dissemination.

with distinct combinations of mutations. According to this hypothesis only a small subpopulation of mutations necessary for metastasis. However, recent experiments, in which gene profiling of primaries has been compared, challenge this hypothesis. For example, a subset of breast cancers has a gene expression pattern in metastases, although no clinical evidence for metastasis is apparent. In these tumors it seems to be a predilection for metastatic spread early, during primary carcinogenesis. Metastases, according to the stochastic generation of metastatic subclones postulated above. It should be noted, however, that the model described above would not detect a small subset of metastatic subclones within a large tumor. Perhaps with aggressive tumors acquiring a metastases-permissive gene expression pattern early in tumor progression and random mutations to complete the metastatic phenotype.

One open question in the field is, are there genes whose principal or sole contribution to tumorigenesis is of more than academic interest, because if altered forms of certain genes promote or inhibit metastasis, detection in a primary tumor would have both prognostic and therapeutic implications. Metastasis involves a variety of steps and pathways described above. It is thought therefore that, unlike transformation, where RB seems to play a key role, genes that function as "metastasis oncogenes" or "metastatic suppressors" are of more interest. Such metastasis oncogenes are SNAIL and TWIST, which encode transcription factors whose principal function is to promote the epithelial-to-mesenchymal transition (EMT). In EMT, carcinoma cells down-regulate certain epithelial markers and up-regulate certain mesenchymal markers (e.g., vimentin and smooth muscle actin). These changes confer a promigratory phenotype that is essential for metastasis. Loss of E-cadherin expression seems to be a common feature of metastatic tumors and TWIST is a transcriptional repressor that promotes EMT by down-regulating E-cadherin expression in breast cancers; whether this is a general phenomenon remains to be established.

## SUMMARY

### Invasion and Metastasis

Ability to invade tissues, a hallmark of malignancy, occurs in four steps: loosening of cell-cell contacts, degradation of ECM, attachment to novel ECM components, and migration. Cell-cell contacts are lost by the inactivation of E-cadherin through a variety of pathways. Cell-matrix contacts are lost by the inactivation of integrins. ECM degradation is mediated by proteolytic enzymes secreted by tumor cells and stromal cells, such as MMPs and cathepsins. Proteolytic enzymes release growth factors sequestered in the ECM and generate chemotactic and angiogenic factors. The metastatic site of many tumors can be predicted by the site of the primary tumor. Many tumors arrest in the first capillary bed they encounter (commonly). Some tumors show organ tropism, probably due to expression of receptors whose ligands are expressed by the metastatic site.

## Genomic Instability-Enabler of Malignancy

In the preceding section we discussed six defining features of malignancy and the genetic alterations that lead to these phenotypic attributes of cancer cells. How do these mutations arise? Although humans are exposed to mutagenic (e.g., chemicals, radiation, sunlight), cancers are relatively rare outcomes of these exposures because of the ability of normal cells to repair DNA damage. The importance of DNA repair in maintaining the integrity of the genome is illustrated by several inherited disorders in which genes that encode proteins involved in DNA repair are defective. *defects in DNA repair proteins are at a greatly increased risk of developing cancer*. Typically, genes involved in DNA repair are lost; however, recent work has suggested that at least a subset of these genes may be overexpressed. Defects in three types of DNA repair systems-mismatch repair, nucleotide excision repair, and telomerase repair are discussed next.

### Hereditary Nonpolyposis Colon Cancer Syndrome

The role of DNA repair genes in predisposition to cancer is illustrated dramatically by hereditary nonpolyposis colon cancer syndrome. This disorder, characterized by familial carcinomas of the colon affecting predominantly the right side of the colon (15), results from defects in genes involved in DNA mismatch repair. When a strand of DNA is being replicated, "proofreaders" check for errors. For example, if there is an erroneous pairing of G with T rather than the normal A with T, the proofreader corrects the error. Without these "proofreaders," errors gradually accumulate in several genes, including proto-oncogenes. Mutations in at least four mismatch repair genes have been found to underlie HNPCC (Ch



inherits one defective copy of one of several DNA mismatch repair genes and acquires the second defective copy. Mismatch repair genes behave like tumor suppressor genes in their mode of inheritance, but in contrast to them, they affect cell growth only indirectly-by allowing mutations in other genes during the process of normal DNA replication. One of the hallmarks of patients with mismatch repair defects is microsatellite instability (MSI). Microsatellites are tandem repeats of short DNA sequences throughout the genome. In normal people, the length of these microsatellites remains constant. However, in patients with mismatch repair defects, microsatellites are unstable and increase or decrease in length. Although HNPCC accounts only for 2% of sporadic colorectal cancers, it is detected in about 15% of sporadic cancers. The growth-regulating genes that are mutated in HNPCC are characterized.

### *Xeroderma Pigmentosum*

Patients with another inherited disorder, xeroderma pigmentosum, are at increased risk for the development of skin cancer due to the ultraviolet (UV) light contained in sun rays. The basis of this disorder is defective DNA repair of pyrimidine residues, preventing normal DNA replication. Such DNA damage is repaired by the nucleotide excision repair pathway. Several proteins are involved in nucleotide excision repair, and an inherited loss of any one can give rise to xeroderma pigmentosum.

### *Diseases with Defects in DNA Repair by Homologous Recombination*

A group of autosomal recessive disorders comprising Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia, are characterized by hypersensitivity to other DNA-damaging agents, such as ionizing radiation (Bloom syndrome and Fanconi anemia) and chemical agents, such as nitrogen mustard (Fanconi anemia). Their phenotype is complex and includes cancer, features such as neural symptoms (ataxia-telangiectasia), anemia (Fanconi anemia), and immunodeficiency (Bloom syndrome). As mentioned earlier, the gene mutated in ataxia-telangiectasia is *ATM*, which seems to be involved in responding to DNA damage caused by ionizing radiation. Evidence for the role of DNA repair genes in the study of hereditary breast cancer. Mutations in two genes, *BRCA1* and *BRCA2*, account for 80% of familial breast cancer. In addition to breast cancer, women with *BRCA1* mutations have a substantially higher risk of epithelial ovarian cancer, men with *BRCA1* mutations have a slightly higher risk of prostate cancer. Likewise, mutations in the *BRCA2* gene increase the risk of breast cancer as well as cancer of the ovary, prostate, pancreas, bile ducts, stomach, and melanocytes. Although the mechanism has not been elucidated fully, cells that lack these genes develop chromosomal breaks and severe aneuploidy, at least in part, in the homologous recombination DNA repair pathway. For example, *BRCA1* is involved in the homologous recombination pathway and is also linked to the ATM checkpoint pathway. *BRCA2* is involved in the homologous recombination pathway and the *BRCA2* protein has been shown to bind to RAD51, a protein involved in the reaction of homologous recombination. Similar to other tumor suppressor genes, both copies of *BRCA1* and *BRCA2* must be mutated for cancer to develop. Although linkage of *BRCA1* and *BRCA2* to familial breast cancers is established, the same is not true for sporadic cases of breast cancer. In this regard, *BRCA1* and *BRCA2* are different from other tumor suppressor genes like *p53*, which are inactivated in both familial and sporadic cancers.

## **SUMMARY**

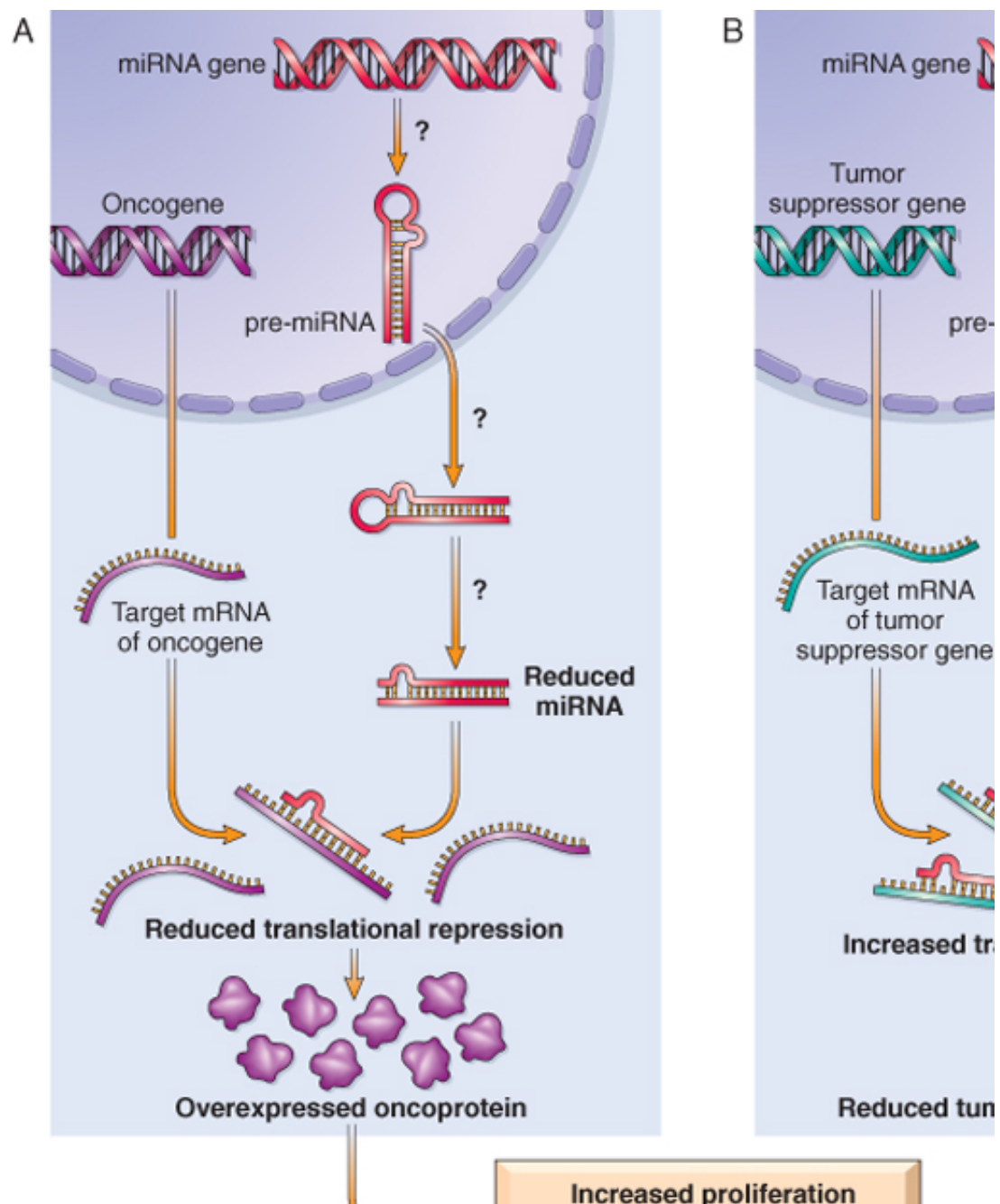
### **Genomic Instability-Enabler of Malignancy**

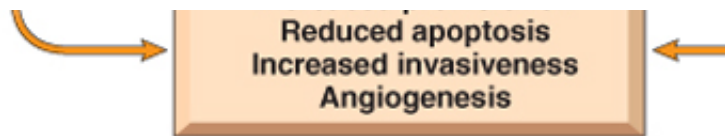
Individuals with inherited mutations of genes involved in DNA repair system have an increased risk of developing cancer. Patients with HNPCC syndrome have a defective mismatch repair system and develop carcinomas of the colon. These patients show microsatellite instability (MSI), in which short repeats throughout the genome change in length. Patients with xeroderma pigmentosum have a defect in the nucleotide excision repair pathway and a predisposition to the development of cancers of the skin exposed to UV light, because of an inability to repair DNA damage caused by UV light. Syndromes involving defects in the homologous recombination DNA repair pathway (Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia) are characterized by hypersensitivity to DNA-damaging agents, such as ionizing radiation and chemical agents. *BRCA1* and *BRCA2*, which are mutated in familial breast cancers, are involved in DNA repair by homologous recombination.

## **MicroRNAs (MiRNAs) and Cancer**

As discussed in [Chapter 7](#), miRNAs are non-coding, single-stranded RNAs, approximately 22 nucleotides in length, that act as negative regulators of genes. They inhibit gene expression post-transcriptionally by repressing translation of the target mRNA.

cleavage. Given that miRNAs control cell growth, differentiation, and cell survival, it is not surprising that they support their role in carcinogenesis. As illustrated by Figure 6-28, miRNAs can participate in neoplasia by either increasing the expression of oncogenes or reducing the expression of tumor suppressor genes. If an miRNA that normally targets an oncogene is downregulated, the expression of the oncogene will increase. Conversely, if an miRNA that normally targets a tumor suppressor gene is overexpressed, the expression of the tumor suppressor gene will decrease. This can lead to increased proliferation and tumor formation. For example, downregulation of miR-15 and miR-16 in leukemias and lymphomas results in increased expression of BCL2, the antiapoptotic gene. Thus, miRNAs behave as tumor suppressor genes. Similar miRNA-mediated upregulation of RAS, and IGF1R in lung tumors and in certain B cell leukemias respectively. In some brain and breast tumors there are certain miRNAs. Although the targets of these miRNAs have not been identified, presumably they are genes whose activities are reduced by the overexpressed miRNA.





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Figure 6-28 Role of miRNAs in tumorigenesis. **A.** Reduced activity of a miRNA that inhibits translation of an oncogene. Overactivity of a miRNA that targets a tumor suppression gene reduces the production of the tumor suppressor protein. These findings indicate that the mechanisms by which changes in the level or activity of miRNA are

These findings not only provide novel insights into carcinogenesis, they also have practical implications. Augmentation of the functions of miRNAs could be useful in chemotherapy. Since miRNAs regulate normal gene expression ("miRNA profiling") can provide clues to the cell of origin and classification of tumors. Identification of these oncogenic miRNAs, or so called "oncomirs."

### Molecular Basis of Multistep Carcinogenesis

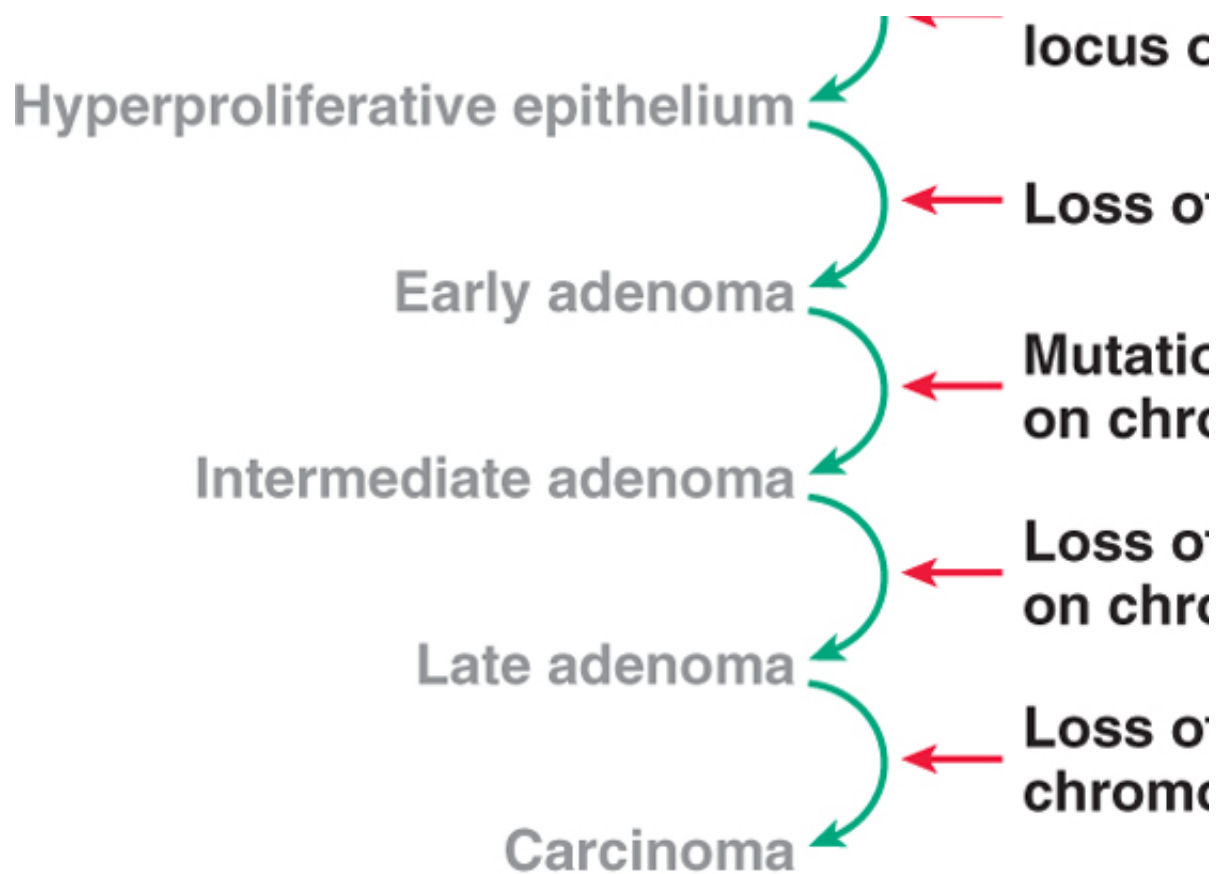
Given that malignant tumors must develop several fundamental abnormalities, discussed above, it is clear that they arise *from accumulation of multiple mutations*. Indeed, recently completed genome-wide analysis of breast tumors shows that individual tumors accumulate an average of 90 mutant genes. A much smaller subset of these ( $\approx 1\%$ ) are frequently included among these are some known oncogenes and tumor suppressor genes, while others are tumor-associated. Each of these alterations represents crucial steps in the progression from a normal cell to a malignant one. Furthermore, *it seems that evolution has installed a variety of "intrinsic tumor-suppressive mechanisms that thwart the actions of growth-promoting mutations*. Indeed, in cells with competent growth-promoting genes like *RAS* leads not to transformation, but to senescence or apoptosis. Thus, emergence of a malignant phenotype requires mutational loss of many genes including those that regulate apoptosis and senescence. A dramatic example of the malignant phenotype is documented by the study of colon carcinoma. These lesions are believed to progress through morphologically identifiable stages: colon epithelial hyperplasia followed by formation of adenoma, which ultimately undergo malignant transformation ([Chapter 15](#)). The proposed molecular correlates of this progression are illustrated in [Figure 6-29](#). According to this scheme, inactivation of the *APC* tumor suppressor gene, followed by activation of *RAS* and, ultimately, loss of a tumor suppressor gene on 18q and loss of *p53*. The precise temporal sequence of these events is different in each organ and tumor type.

### Karyotypic Changes in Tumors

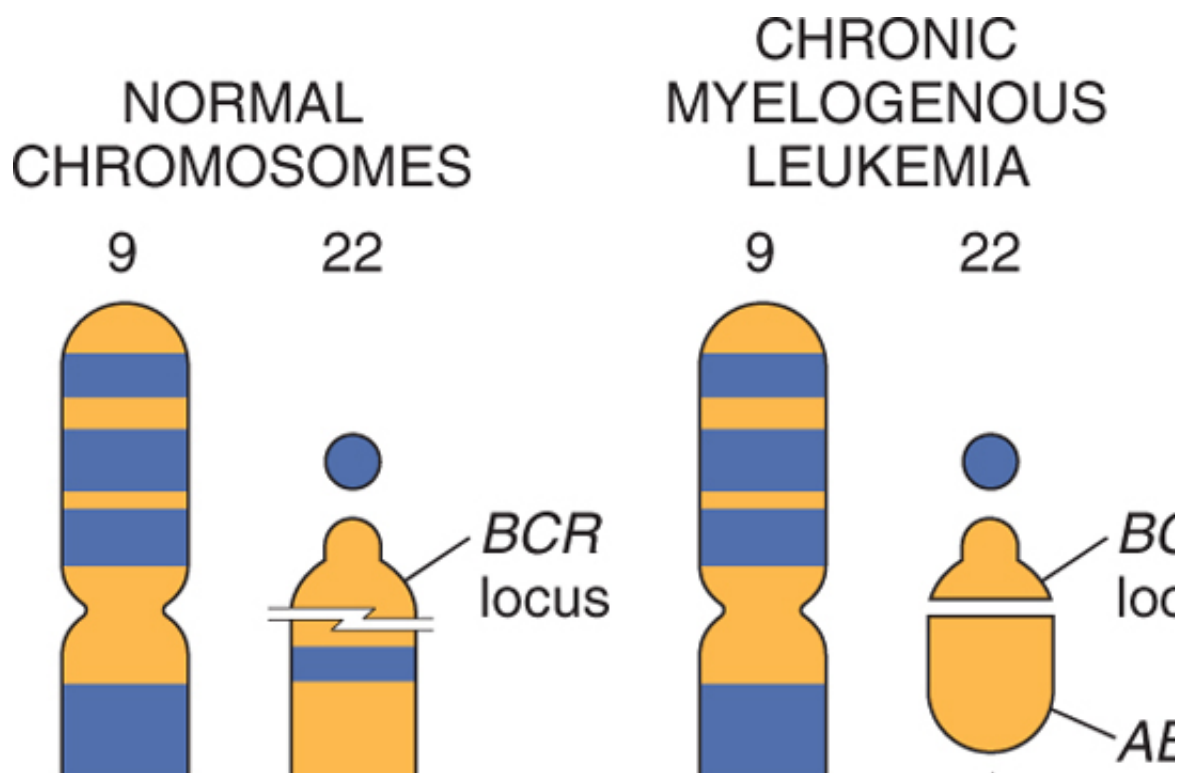
The genetic damage that activates oncogenes or inactivates tumor suppressor genes may be subject to detection in a karyotype. As previously discussed, the *RAS* oncogene represents the best example. In certain neoplasms, karyotypic abnormalities are nonrandom and common. Specific abnormalities are characteristic of leukemias and lymphomas, and in an increasing number of nonhematopoietic tumors. The common types of chromosomal changes in tumor cells are (1) balanced translocations, (2) deletions, and (3) cytogenetic manifestations of genomic instability. Chromosomes may be gained or lost, termed aneuploidy.

#### Balanced Translocations

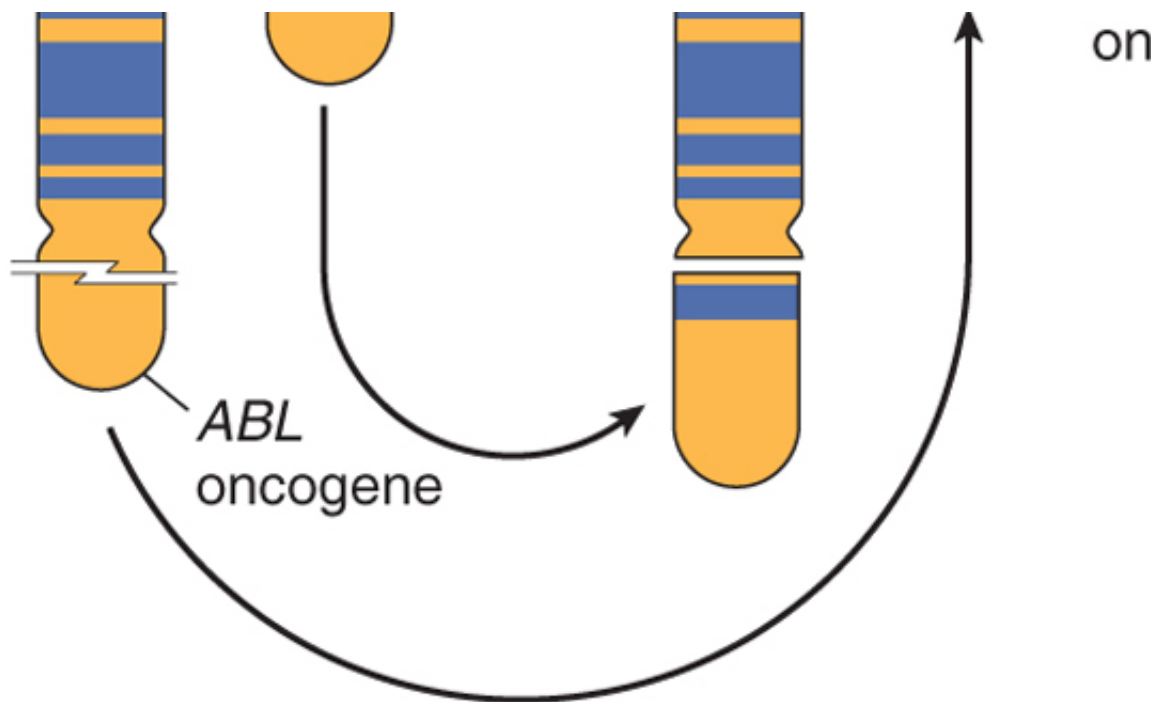




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 Figure 6-29 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. (f  
 genetic model of colorectal carcinogenesis. Cell 61:759, 1990.)







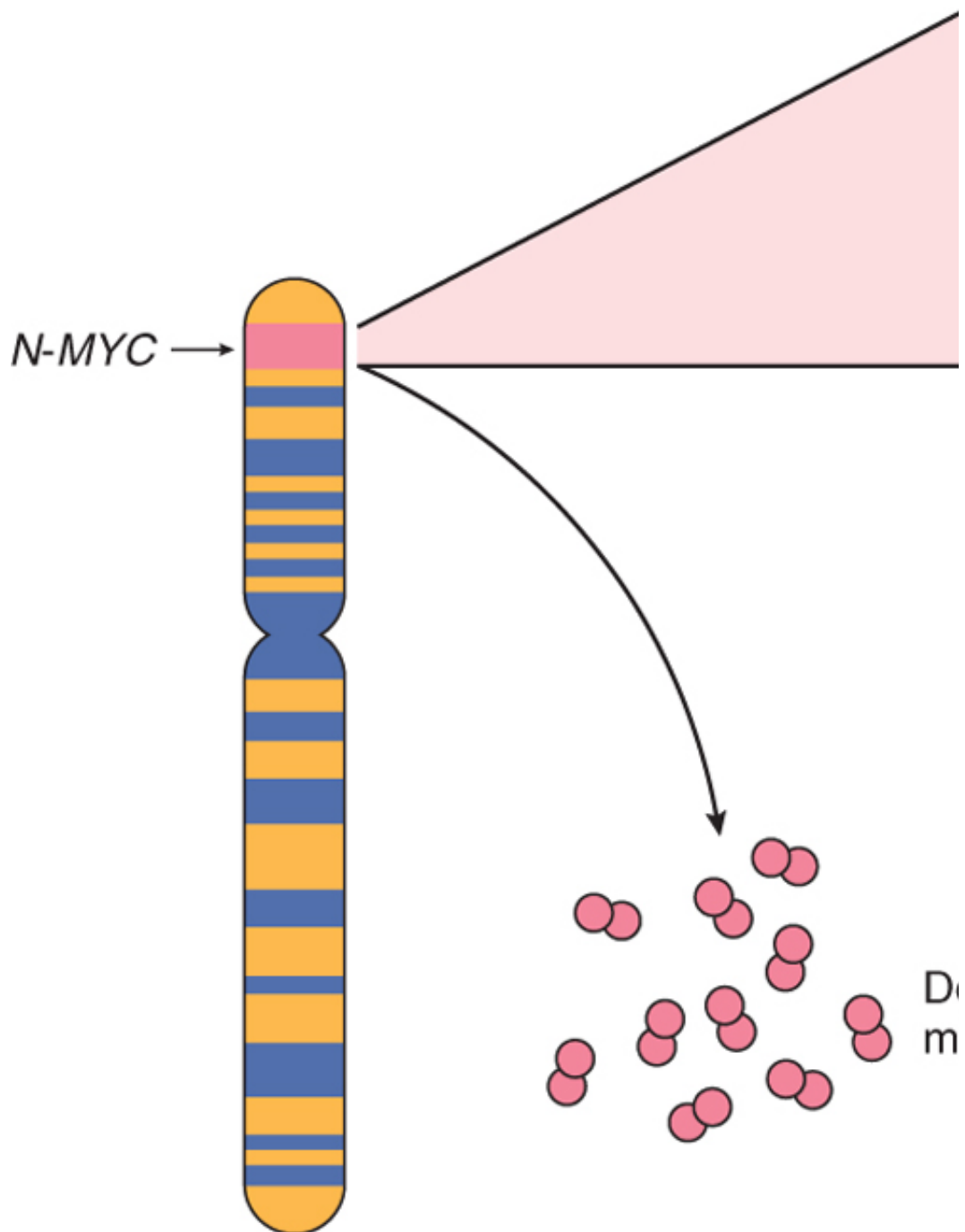
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Figure 6-30 The chromosomal translocation and associated oncogene in chronic myeloid leukemia

Balanced translocations are extremely common, especially in hematopoietic neoplasms. Translocations can occur in two ways. First, specific translocations can result in overexpression of proto-oncogenes by removing regulatory elements and placing them under control of an inappropriate promoter. Second, translocations can rearrange the DNA sequence of two unrelated genes in new ways. This results in the expression of growth-promoting proteins. The Philadelphia (Ph) chromosome in chronic myeloid leukemia, comprising a reciprocal and balanced translocation between chromosomes 22 and, usually, 9 (Fig. 6-30). As a consequence, chromosome 22 appears abbreviated. *More than 90% of cases of chronic myeloid leukemia, is a reliable marker of the disease. The few cases of chronic myeloid leukemia show molecular evidence of the BCR-ABL rearrangement, the crucial change mentioned earlier, such changes give rise to the BCR-ABL fusion gene with potent tyrosine kinase activity. In Burkitt lymphoma the cells have a translocation, usually between chromosomes 8 and 14. This leads to the juxtaposition of chromosome 8 by juxtaposition with immunoglobulin heavy chain gene on chromosome 14. In follicular lymphoma, a reciprocal translocation between chromosomes 14 and 18 leads to overexpression of the BCL2 gene on chromosome 18.*

Hematopoietic cells are most commonly the targets of such translocations, probably because they are active during the processes of antibody or T-cell receptor recombination. However, several solid tumors have recurrent translocations, such as the t(11;22)(q24;q12) translocation in Ewing sarcoma that results in the fusion of EWS and FLI-1. Recently, a subset of prostate cancers has been shown to possess a fusion protein between the ETS family of transcription factors.

### Deletions

Chromosomal deletions are the second most prevalent structural abnormality in tumor cells. *Common deletions are more common in nonhematopoietic solid tumors.* As discussed, deletions of chromosome 13q are common in many tumors. Deletions of 17p, 5q, and 18q have all been noted in colorectal cancers; these regions harbor the APC gene. Deletion of 13p, noted in several tumors, is extremely common in small-cell lung carcinomas, and the hunt is on for genes at this locale.



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Figure 6-31 Amplification of the *N-MYC* gene in human neuroblastoma. The *N-MYC* gene, present normally on chromosome 2, can be amplified either as extra chromosomal double minutes or as a chromosomally integrated homogeneous-staining region (HSR), such as 4, 9, or 13. (Modified from Brodeur GM, et al.: Clinical implication of oncogene activation in human neuroblastoma. In: Brodeur GM, et al.: Neuroblastoma. In: Principles and Practice of Pediatric Oncology, 2nd ed. Philadelphia, PA: JB Lippincott, 1995, pp 100-101. With permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc)

### Gene Amplifications

There are two karyotypic manifestations of gene amplification: homogeneously staining regions or double minutes (Fig. 6-31), which are seen as small paired fragments of chromatin. Neuroblastomas and gliomas are examples of gene amplification involving the *N-MYC* and *HER-2/NEU* genes respectively.

### Epigenetic Changes

Epigenetics concerns reversible, heritable changes in gene expression that occur without mutation. In a few years that certain tumor suppressor genes may be inactivated, not because of structural changes but because of hypermethylation of promoter sequences. For example, *p14ARF* is silenced in colon and stomach cancers. Furthermore, *BRCA1* in breast cancer, *VHL* in renal cell cancer, and the *MLH1* and *MSH2* genes in colorectal cancer are frequently silenced by methylation of the promoter. Interestingly, although these genes are hypermethylated in tumor cells, the entire genome seems to be hypomethylated compared to normal cells. Hypomethylation has been shown to cause chromosomal instability and can induce tumors in mice. Epigenetic changes in carcinogenesis occur in many ways.

## SUMMARY

### Karyotypic Changes in Tumors

Tumor cells may develop a variety of nonrandom chromosomal abnormalities that contribute to malignancy; these include balanced translocations, deletions, and cytogene amplification. Balanced translocations contribute to carcinogenesis by overexpression of oncogenes and underexpression of tumor suppressor genes. Deletions of tumor suppressor genes, whereas gene amplification increases the expression of oncogenes. Epigenetic changes in gene expression also occur, not by mutation but by reversible, heritable changes in gene expression that occur, not by mutation but by methylation of the promoter.



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## ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

Genetic damage lies at the heart of carcinogenesis. What agents inflict such damage? Three classes of carcinogenic agents can be identified: (1) chemicals, (2) radiant energy, and (3) microbial agents. Chemicals and radiant energy are documented causes of cancer in humans, and oncogenic viruses are involved in the pathogenesis of tumors in several animal models and at least in some human tumors. In the following discussion, each class of agents is considered separately, but it is important to note that several may act in concert or sequentially to produce the multiple genetic abnormalities characteristic of neoplastic cells.

### Chemical Carcinogens

More than 200 years ago, the London surgeon Sir Percival Pott correctly attributed scrotal skin cancer in chimney sweeps to chronic exposure to soot. Based on this observation, the Danish Chimney Sweeps Guild ruled that its members must bathe daily. No public health measure since that time has achieved so much in the control of a form of cancer. Subsequently, hundreds of chemicals have been shown to be carcinogenic in animals.

Some of the major agents are presented in [Table 6-4](#). A few comments are offered on a handful of these.

### Direct-Acting Agents

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**Table 6-4. Major Chemical Carcinogens**

<b>Direct-Acting Carcinogens</b>
<b>ALKYLATING AGENTS</b>
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide <sub>Rx</sub> , chlorambucil <sub>Rx</sub> , nitrosoureas, and others)
<b>ACYLATING AGENTS</b>
1-Acetyl-imidazole
Dimethylcarbamyl chloride
<b>Procarcinogens That Require Metabolic Activation</b>
<b>POLYCYCLIC AND HETEROCYCLIC AROMATIC HYDROCARBONS</b>
Benz(a)anthracene
Benzo(a)pyrene
Dibenz(a, h)anthracene
3-Methylcholanthrene
7, 12-Dimethylbenz(a)anthracene
<b>AROMATIC AMINES, AMIDES, AZO DYES</b>
2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)
<b>Natural Plant and Microbial Products</b>
Aflatoxin B <sub>1</sub>



Griseofulvin <sup>®</sup>
Cycasin
Safrole
Betel nuts
<b>OTHERS</b>
Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

Direct-acting agents require no metabolic conversion to become carcinogenic. They are in general weak carcinogens but are important because some of them are cancer chemotherapeutic drugs (e.g., alkylating agents) that have successfully cured, controlled, or delayed recurrence of certain types of cancer (e.g., leukemia, lymphoma, Hodgkin lymphoma, and ovarian carcinoma), only to evoke later a second form of cancer, usually leukemia. This situation is even more tragic when their initial use has been for non-neoplastic disorders, such as rheumatoid arthritis or Wegener granulomatosis. The risk of induced cancer is low, but its existence dictates judicious use of such agents.

### ***Indirect-Acting Agents***

The designation *indirect-acting agent* refers to chemicals that require metabolic conversion to an *ultimate carcinogen* before they become active. Some of the most potent indirect chemical carcinogens—the polycyclic hydrocarbons—are present in fossil fuels. For example, benzo[a]pyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking. *These products are implicated in the causation of lung cancer in cigarette smokers.* Polycyclic hydrocarbons may also be produced from animal fats during the process of broiling meats and are present in smoked meats and fish. The principal active products in many hydrocarbons are epoxides, which form covalent adducts (addition products) with molecules in the cell, principally DNA, but also with RNA and proteins.

The aromatic amines and azo dyes are another class of indirect-acting carcinogens. Before its carcinogenicity was recognized, β-naphthylamine was responsible for a 50-fold increased incidence of bladder cancers in heavily exposed workers in the aniline dye and rubber industries. Many other occupational carcinogens were listed in Table 6-2. Because indirect-acting carcinogens require metabolic activation for their conversion to DNA-damaging agents, much interest is focused on the enzymatic pathways that are involved, such as the cytochrome P-450-dependent monooxygenases. The genes that encode these enzymes are polymorphic, and enzyme activity varies among different individuals. It is widely believed that the susceptibility to chemical carcinogenesis depends at least in part on the specific allelic form of the enzyme inherited. Thus, it may be possible in the future to assess cancer risk in a given individual by genetic analysis of such enzyme polymorphisms.

A few other agents merit brief mention. Aflatoxin B<sub>1</sub> is of interest because it is a naturally occurring agent produced by some strains of *Aspergillus*, a mold that grows on improperly stored grains and nuts. There is a *strong correlation between the dietary level of this food contaminant and the incidence of hepatocellular carcinoma in some parts of Africa and the Far East.* Additionally, vinyl chloride, arsenic, nickel, chromium, insecticides, fungicides, and polychlorinated biphenyls are potential carcinogens in the workplace and about the house. Finally, nitrites used as food preservatives have caused concern, since they cause nitrosylation of amines contained in the food. The nitrosoamines so formed are suspected to be carcinogenic.

### ***Mechanisms of Action of Chemical Carcinogens***

Because malignant transformation results from mutations, it should come as no surprise that most chemical carcinogens are mutagenic. Indeed, all direct and ultimate carcinogens contain

most chemical carcinogens are mutagenic. Indeed, all direct and ultimate carcinogens contain highly reactive electrophile groups that form chemical adducts with DNA, as well as with proteins and RNA. Although any gene may be the target of chemical carcinogens, the commonly mutated oncogenes and tumor suppressors, such as *RAS* and *p53*, are important targets of chemical carcinogens. Indeed, specific chemical carcinogens, such as aflatoxin B<sub>1</sub>, produce characteristic mutations in the *p53* gene, such that detection of the "*signature mutation*" within the *p53* gene establishes aflatoxin as the causative agent. These associations are proving useful tools in epidemiologic studies of chemical carcinogenesis.

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Carcinogenicity of some chemicals is augmented by subsequent administration of *promoters* (e.g., phorbol esters, hormones, phenols, and drugs) that by themselves are nontumorigenic. To be effective, repeated or sustained exposure to the promoter must *follow* the application of the mutagenic chemical, or *initiator*. The initiation-promotion sequence of chemical carcinogenesis raises an important question: Since promoters are not mutagenic, how do they contribute to tumorigenesis? Although the effects of tumor promoters are pleiotropic, *induction of cell proliferation is a sine qua non of tumor promotion*. It seems most likely that while the application of an initiator may cause the mutational activation of an oncogene such as *RAS*, subsequent application of promoters leads to clonal expansion of initiated (mutated) cells. Forced to proliferate, the initiated clone of cells accumulates additional mutations, developing eventually into a malignant tumor. Indeed, the concept that sustained cell proliferation increases the risk of mutagenesis, and hence neoplastic transformation, is also applicable to human carcinogenesis. For example, pathologic hyperplasia of the endometrium (Chapter 19) and increased regenerative activity that accompanies chronic liver cell injury are associated with the development of cancer in these organs. Were it not for the DNA repair mechanisms discussed earlier, the incidence of chemically induced cancers in all likelihood would be much higher. As mentioned above, the rare hereditary disorders of DNA repair, including xeroderma pigmentosum, are associated with greatly increased risk of cancers induced by UV light and certain chemicals.

## SUMMARY

### Chemical Carcinogens

Chemical carcinogens have highly reactive electrophile groups that directly damage DNA, leading to mutations and eventually cancer. Direct-acting agents do not require metabolic conversion to become carcinogenic, while indirect-acting agents are not active until converted to an ultimate carcinogen by endogenous metabolic pathways. Hence polymorphisms of endogenous enzymes like cytochrome P-450 may influence carcinogenesis. Following exposure of a cell to a mutagen or an initiator, tumorigenesis can be enhanced by exposure to promoters, which stimulate proliferation of the mutated cells. Examples of human carcinogens include direct-acting (e.g., alkylating agents used for chemotherapy), indirect-acting (e.g., benzopyrene, azo dyes, and aflatoxin), and promoters/agents that cause pathologic hyperplasias of liver, endometrium.

### Radiation Carcinogenesis

Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen. Unprotected miners of radioactive elements have a 10-fold increased incidence of lung cancers. Follow-up of survivors of the atomic bombs dropped on Hiroshima and Nagasaki disclosed a markedly increased incidence of leukemia—principally acute and chronic myeloid leukemia—after an average latent period of about 7 years, as well as an

increased mortality rate from thyroid, breast, colon, and lung carcinomas. The nuclear power accident at Chernobyl in the former Soviet Union continues to exact its toll in the form of high cancer incidence in the surrounding areas. Therapeutic irradiation of the head and neck can give rise to papillary thyroid cancers years later. The oncogenic properties of ionizing radiation are related to its mutagenic effects; it causes chromosome breakage, translocations, and, less frequently, point mutations. Biologically, double-stranded DNA breaks seem to be the most important form of DNA damage caused by radiation. There is also some evidence that nonlethal doses of radiation may induce genomic instability, favoring carcinogenesis.

The oncogenic effect of UV rays merits special mention because it highlights the importance of DNA repair in carcinogenesis. Natural UV radiation derived from the sun can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas). At greatest risk are fair-skinned people who live in locales such as Australia and New Zealand that receive a great deal of sunlight. Nonmelanoma skin cancers are associated with total cumulative exposure to UV radiation, whereas melanomas are associated with intense intermittent exposure—as occurs with sunbathing. UV light has several biologic effects on cells. Of particular relevance to carcinogenesis is the ability to damage DNA by forming pyrimidine dimers. This type of DNA damage is repaired by the nucleotide excision repair pathway. With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results. As mentioned above, patients with the inherited disease *xeroderma pigmentosum* have a defect in the nucleotide excision repair pathway. As expected, there is a greatly increased predisposition to skin cancers in this disorder.

#### **SUMMARY**

##### **Radiation Carcinogenesis**

Ionizing radiation causes chromosome breakage, translocations, and, less frequently, point mutations, leading to genetic damage and carcinogenesis. UV rays induce the formation of pyrimidine dimers within DNA, leading to mutations. Therefore UV rays can give rise to squamous cell carcinomas and melanomas of the skin.

## **Viral and Microbial Oncogenesis**

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Many DNA and RNA viruses have proved to be oncogenic in animals as disparate as frogs and primates. Despite intense scrutiny, however, only a few viruses have been linked with human cancer. Our discussion focuses on human oncogenic viruses. Also discussed is the emerging role of the bacterium *H. pylori* in gastric cancer.

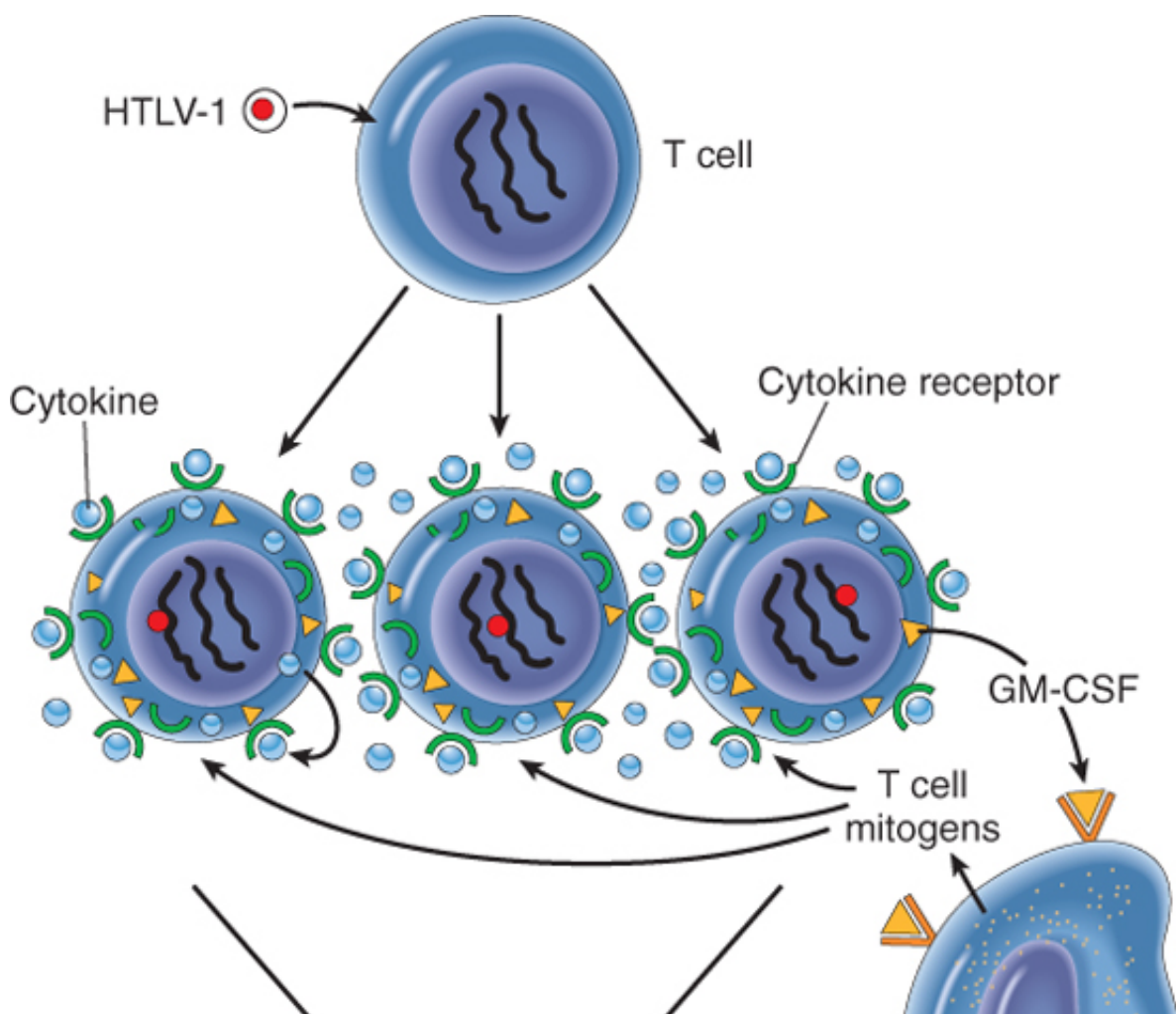
### **Oncogenic RNA Viruses**

The study of oncogenic retroviruses in animals has provided spectacular insights into the genetic basis of cancer. However, human T-cell leukemia virus-1 (HTLV-1) is the only retrovirus that has been demonstrated to cause cancer in humans. HTLV-1 is associated with a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin but is found sporadically elsewhere, including the United States. Similar to the human immunodeficiency virus (HIV), HTLV-1 has tropism for CD4<sup>+</sup> T cells, and this subset of T cells is the major target for neoplastic transformation. Human infection requires transmission of infected T cells via sexual intercourse, blood products, or breastfeeding. Leukemia develops only in about 3% to 5% of infected individuals after a long latent period of 20 to 50 years.

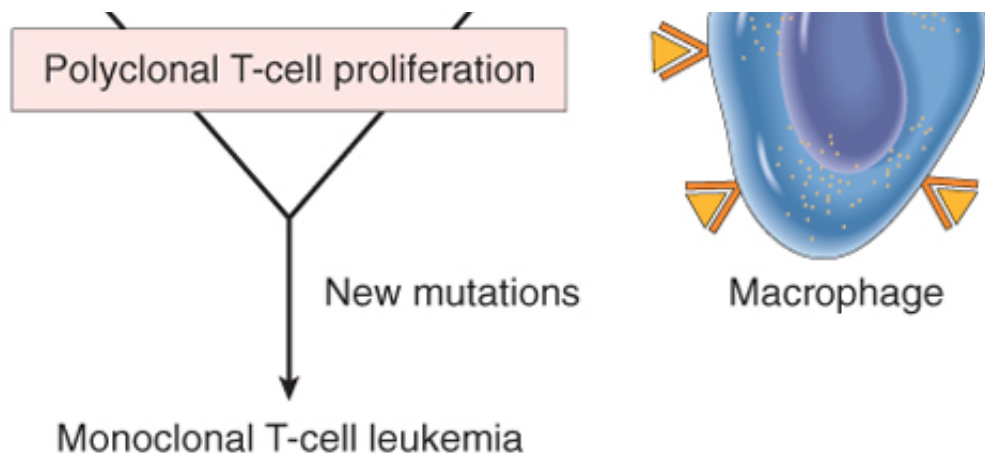
There is little doubt that HTLV-1 infection of T lymphocytes is necessary for leukemogenesis, but the molecular mechanisms of transformation are not clear. HTLV-1 does not contain a *viral oncogene*, and in contrast to certain animal retroviruses, no consistent integration site next to a cellular oncogene has been discovered. Indeed, the long latency period between initial infection

cellular oncogene has been discovered. Indeed, the long latency period between initial infection and development of disease suggests a multistep process, during which many oncogenic mutations are accumulated.

The genome of HTLV-1 contains, in addition to the usual retroviral genes, a unique region called *pX*. This region encodes several genes, including one called *TAX*. The *TAX* protein has been shown to be necessary and sufficient for cellular transformation. By interacting with several transcription factors, such as NF- $\kappa$ B, the *TAX* protein can transactivate the expression of genes that encode cytokines, cytokine receptors, and costimulatory molecules. This inappropriate gene expression leads to autocrine signaling loops and increased activation of pro-mitogenic signaling cascades. Furthermore, *TAX* can drive progression through the cell cycle by directly binding to and activating cyclins. In addition, *TAX* can repress the function of several tumor suppressor genes that control the cell cycle, including *CDKN2A/p16* and *p53*. From these and other observations the following scenario is emerging (Fig. 6-32): The *TAX* gene turns on several cytokine genes and their receptors (IL-2 and IL-2R, IL-15, and IL-15R), setting up an autocrine system that drives T-cell proliferation. Of these cytokines, IL-15 seems to be more important, but much remains to be defined. Additionally, a parallel paracrine pathway is activated by increased production of granulocyte-macrophage colony-stimulating factor, which stimulates neighboring macrophages to produce other T-cell mitogens. Initially the T-cell proliferation is polyclonal because the virus infects many cells, but, because of *TAX*-based inactivation of tumor suppressor genes such as *p53*, the proliferating T cells are at increased risk of secondary transforming events (mutations), which lead ultimately to the outgrowth of a monoclonal neoplastic T-cell population.







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Figure 6-32 Pathogenesis of human T-cell lymphotropic virus (HTLV-1)-induced T-cell leukemia/lymphoma. HTLV-1 infects many T cells and initially causes polyclonal proliferation by autocrine and paracrine pathways triggered by the TAX gene. Simultaneously, TAX neutralizes growth-inhibitory signals by affecting *p53* and *CDKN2A/p16* genes. Ultimately, a monoclonal T-cell leukemia/lymphoma results when one proliferating T cell suffers additional mutations.

## SUMMARY

### Oncogenic RNA Viruses

HTLV-1 causes a T-cell leukemia that is endemic in Japan and the Caribbean. HTLV-1 encodes a viral TAX protein, which turns on genes for cytokines and their receptors in infected T cells. This sets up autocrine and paracrine signaling loops that stimulate T-cell proliferation. Although this proliferation is initially polyclonal, the proliferating T cells are at increased risk of secondary mutations that lead to the outgrowth of a monoclonal leukemia.

### Oncogenic DNA Viruses

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As with RNA viruses, several oncogenic DNA viruses that cause tumors in animals have been identified. Four DNA viruses—human papillomavirus (HPV), Epstein-Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus 8), and hepatitis B virus (HBV)—are of special interest, because they are strongly associated with human cancer. KSHV and Kaposi sarcoma were discussed in [Chapter 5](#). The others are presented here.

#### Human Papillomavirus

Scores of genetically distinct types of HPV have been identified. Some types (e.g., 1, 2, 4, and 7) definitely cause benign squamous papillomas (warts) in humans ([Chapters 19](#) and [22](#)). By contrast, high-risk HPVs (e.g., 16 and 18) have been implicated in the genesis of several cancers, particularly squamous cell carcinoma of the cervix and anogenital region. In addition, at least 20% of oropharyngeal cancers are associated with HPV. In contrast to cervical cancers, genital warts have low malignant potential and are associated with low-risk HPVs predominantly HPV-6 and HPV-11.

The oncogenic potential of HPV can be related to products of two early viral genes, E6 and E7. Together, they interact with a variety of growth-regulating proteins encoded by protooncogenes and tumor suppressor genes. The E7 protein binds to the retinoblastoma protein and displaces the E2F transcription factors that are normally sequestered by RB, promoting progression through the cell cycle. Interestingly, E7 protein from high-risk HPV types has a higher affinity for

RB than does E7 from low-risk HPV types. E7 also inactivates the CDKs CDKN1A/p21 and CDKN1B/p27. E7 proteins from high-risk HPV types (types 16, 18, and 31) also bind and presumably activate cyclins E and A. The E6 protein has complementary effects. It binds to and mediates the degradation of p53 and BAX, a pro-apoptotic member of the BCL2 family, and it activates telomerase. In analogy with E7, E6 from high-risk HPV types has a higher affinity for p53 than E6 from low-risk HPV types. Interestingly, in benign warts the HPV genome is maintained in a nonintegrated episomal form, while in cancers the HPV genome is randomly integrated into the host genome. Integration interrupts the viral DNA, resulting in overexpression of the oncoproteins E6 and E7. Furthermore, cells in which the viral genome has integrated show significantly more genomic instability.

To summarize, *infection with high-risk HPV types simulates the loss of tumor suppressor genes, activates cyclins, inhibits apoptosis, and combats cellular senescence*. Thus, it is evident that many of the hallmarks of cancer discussed earlier are driven by HPV proteins. However, infection with HPV itself is not sufficient for carcinogenesis. For example, when human keratinocytes are transfected with DNA from HPV 16, 18, or 31 in vitro, they are immortalized, but they do not form tumors in experimental animals. Cotransfection with a mutated *RAS* gene results in full malignant transformation. These data strongly suggest that HPV, in all likelihood, acts in concert with other environmental factors ([Chapter 19](#)). However, the primacy of HPV infection in the causation of cervical cancer is attested to by the near complete protection from this cancer by anti-HPV vaccines.

### **Epstein-Barr Virus**

EBV has been implicated in the pathogenesis of several human tumors: Burkitt lymphoma, B-cell lymphomas in patients with acquired immunodeficiency syndrome and other causes of immunosuppression, a subset of Hodgkin lymphoma, and nasopharyngeal carcinoma. Except for nasopharyngeal carcinoma, all others are B-cell tumors. A subset of T-cell lymphomas and the rare NK-cell lymphomas may also be related to EBV.

Burkitt lymphoma is endemic in certain parts of Africa and is sporadic elsewhere. In endemic areas, tumor cells in virtually all patients carry the EBV genome. The molecular basis of B-cell proliferations induced by EBV is complex. EBV uses the complement receptor, CD21, to attach to and infect B cells. In vitro such infection leads to polyclonal B-cell proliferation and generation of B-lymphoblastoid cell lines. One of the EBV-encoded genes, called *LMP-1*, acts as an oncogene, and its expression in transgenic mice induces B-cell lymphomas. *LMP-1* promotes B-cell proliferation by activating signaling pathways, such as NF- $\kappa$ B and JAK/STAT, which mimic B-cell activation via the B-cell surface molecule CD40. Concurrently, *LMP-1* prevents apoptosis by activating BCL2. Thus, the virus "borrows" a normal B-cell activation pathway to promote its own replication by expanding the pool of cells susceptible to infection. Another EBV-encoded gene, *EBNA-2*, transactivates several host genes, including cyclin D and the *src* family genes. In addition, the EBV genome contains a viral cytokine, vIL-10, that was pirated from the host genome. This viral cytokine can prevent macrophages and monocytes from activating T cells and is required for EBV-dependent transformation of B cells.

In immunologically normal individuals, EBV-driven polyclonal B-cell proliferation in vivo is readily controlled, and the individual either remains asymptomatic or develops a self-limited episode of infectious mononucleosis ([Chapter 12](#)). Evasion of the immune system seems to be a key step in EBV-related oncogenesis. In regions of the world where Burkitt lymphoma is endemic, concomitant (endemic) malaria (or other infections) impair immune competence, allowing sustained B-cell proliferation. Interestingly, although *LMP-1* is the primary transforming oncogene in the EBV genome, it is not expressed in EBV-derived Burkitt lymphoma, because it is also one of the major viral antigens recognized by the immune system. Presumably, infected cells expressing viral antigens such as LMP-1 are kept in check by the immune system. Lymphoma cells emerge only when additional mutations, such as the t(8;14) translocation, a consistent feature of this tumor, activate the *MYC* oncogene. *MYC* activation may substitute for

*LMP-1* signaling, allowing the tumor cells to down-regulate *LMP-1* and evade the immune system. In keeping with this scenario, EBV-derived B-cell lymphomas from immunocompromised patients, discussed below, retain expression of *LMP-1*. It should be noted that in nonendemic areas, 80% of tumors do not harbor the EBV genome, but all tumors possess the specific t(8 ; 14) translocation. This observation suggests that, although non-African Burkitt lymphomas are triggered by mechanisms other than EBV, they develop cancer by similar pathways.

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In immunosuppressed patients, including those with HIV disease and organ transplant recipients, EBV-infected B cells undergo polyclonal expansion, producing lymphoblastoid-like cells. In contrast to Burkitt lymphoma, the B lymphoblasts in immunosuppressed patients do express viral antigens, such as *LMP-1*, that are recognized by T cells. These potentially lethal proliferations can be subdued if the immunologic status of the host improves, as may occur with withdrawal of immunosuppressive drugs in transplant recipients.

Nasopharyngeal carcinoma is endemic in southern China and some other locales, and the EBV genome is found in all tumors. *LMP-1* is expressed in epithelial cells as well. In these cells, as in B cells, *LMP-1* activates the NF- $\kappa$ B pathway. Furthermore, *LMP-1* induces the expression of pro-angiogenic factors such as VEGF, FGF-2, MMP-9, and COX2, which may contribute to oncogenesis. As in Burkitt lymphoma, EBV acts in concert with other, unidentified, factors (Chapter 13).

## **SUMMARY**

### **Oncogenic DNA Viruses**

HPV has been associated with benign warts, as well as cervical cancer. The oncogenic ability of HPV is related to the expression of two viral oncoproteins, E6 and E7; they bind to RB and p53, respectively, neutralizing their function; they also activate cyclins. E6 and E7 from high-risk HPV (that give rise to cancers) have higher affinity for their targets than E6 and E7 from low-risk HPV (that give rise to low-grade tumors). EBV has been implicated in the pathogenesis of Burkitt lymphomas, lymphomas in immunosuppressed individuals with HIV infection or organ transplantation, some forms of Hodgkin lymphoma, and nasopharyngeal carcinoma. All except the nasopharyngeal cancers are B-cell tumors. Certain EBV gene products contribute to oncogenesis by stimulating a normal B-cell proliferation pathway. Concomitant compromise of immune competence allows sustained B-cell proliferation and eventually development of lymphoma with occurrence of additional mutations such as t(8 ; 14), leading to activation of the *MYC* gene.

### **Hepatitis B and Hepatitis C Viruses**

The epidemiologic evidence linking chronic HBV and hepatitis C virus (HCV) infection with hepatocellular carcinoma is strong (Chapter 16). It is estimated that 70% to 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV. However, the mode of action of these viruses in tumorigenesis is not fully elucidated. The HBV and HCV genomes do not encode any viral oncoproteins, and although the HBV DNA is integrated within the human genome, there is no consistent pattern of integration in liver cells. Indeed, the oncogenic effects of HBV and HCV are multifactorial, but the dominant effect seems to be immunologically mediated chronic inflammation with hepatocyte death leading to regeneration, and genomic damage. Although the immune system is generally thought to be protective, recent work has

demonstrated that in the setting of unresolved chronic inflammation, as occurs in viral hepatitis or chronic gastritis caused by *H. pylori* (see below), the immune response may become maladaptive, promoting tumorigenesis.

As with any cause of hepatocellular injury, chronic viral infection leads to the compensatory proliferation of hepatocytes. This regenerative process is aided and abetted by a plethora of growth factors, cytokines, chemokines, and other bioactive substances produced by activated immune cells that promote cell survival, tissue remodeling, and angiogenesis. The activated immune cells also produce other mediators, such as reactive oxygen species, that are genotoxic and mutagenic. One key molecular step seems to be activation of the NF- $\kappa$ B pathway in hepatocytes caused by mediators derived from the activated immune cells. Activation of the NF- $\kappa$ B pathway within hepatocytes blocks apoptosis, allowing the dividing hepatocytes to incur genotoxic stress and to accumulate mutations. Although this seems to be the dominant mechanism in the pathogenesis of viral-induced hepatocellular carcinoma, both HBV and HCV also contain proteins within their genomes that may more directly promote the development of cancer. The HBV genome contains a gene known as *HBx*, and mice transgenic for this gene develop hepatocellular cancers. *HBx* can directly or indirectly activate a variety of transcription factors and several signal transduction pathways. In addition, viral integration can cause secondary rearrangements of chromosomes, including multiple deletions that may harbor unknown tumor suppressor genes.

Though not a DNA virus, HCV is also strongly linked to the pathogenesis of liver cancer. The molecular mechanisms used by HCV are less well defined than are those of HBV. In addition to chronic liver cell injury and compensatory regeneration, components of the HCV genome, such as the HCV core protein may have a direct effect on tumorigenesis, possibly by activating a variety of growth-promoting signal transduction pathways.

## SUMMARY

### Hepatitis B and Hepatitis C Viruses

Between 70% and 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV. The oncogenic effects of HBV and HCV are multifactorial, but the dominant effect seems to be immunologically mediated chronic inflammation, hepatocellular injury, stimulation of hepatocyte proliferation, and production of reactive oxygen species that can damage DNA. The *HBx* protein of HBV and the HCV core protein can activate a variety of signal transduction pathways that may also contribute to carcinogenesis.

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### *Helicobacter pylori*

First incriminated as a cause of peptic ulcers, *H. pylori* now has acquired the dubious distinction of being the first bacterium classified as a carcinogen. Indeed, *H. pylori* infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.

The scenario for the development of gastric adenocarcinoma is similar to that of HBV- and HCV-induced liver cancer. It involves increased epithelial cell proliferation in a background of chronic inflammation. As in viral hepatitis, the inflammatory milieu contains numerous genotoxic agents, such as reactive oxygen species. There is an initial development of chronic inflammation/gastritis, followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer. This sequence takes decades to complete and occurs in only 3% of infected patients. Like HBV and HCV, the *H. pylori* genome also contains genes directly implicated in oncogenesis. Strains associated with gastric adenocarcinoma have been shown to contain a "pathogenicity island" that contains cytotoxin-associated A (*CagA*) gene. Although *H.*



*pylori* is noninvasive, *CagA* is injected into gastric epithelial cells, where it has a variety of effects, including the initiation of a signaling cascade that mimics unregulated growth factor stimulation.

As mentioned above, *H. pylori* is associated with an increased risk for the development of gastric lymphomas as well. The gastric lymphomas are of B-cell origin, and because the transformed B cells normally reside in the marginal zones of lymphoid follicles, these tumors are also called MALT lymphomas (marginal zone-associated lymphomas; [Chapter 12](#)). Their molecular pathogenesis is incompletely understood but seems to involve strain-specific *H. pylori* factors, as well as host genetic factors, such as polymorphisms in the promoters of inflammatory cytokines such as IL-1 $\beta$  and tumor necrosis factor (TNF). It is thought that *H. pylori* infection leads to the formation of *H. pylori*-reactive T cells, which in turn cause polyclonal B-cell proliferations. In time, a monoclonal B-cell tumor emerges in the proliferating B cells, perhaps as a result of accumulation of mutations in growth-regulatory genes. In keeping with this, early in the course of disease, eradication of *H. pylori* "cures" the lymphoma by removing antigenic stimulus for T cells.

## SUMMARY

### *Helicobacter pylori*

*H. pylori* infection has been implicated in both gastric adenocarcinoma and MALT lymphoma. The mechanism of *H. pylori*-induced gastric cancers is multifactorial, including immunologically mediated chronic inflammation, stimulation of gastric cell proliferation, and production of reactive oxygen species that damage DNA. *H. pylori* pathogenicity genes, such as *CagA*, may also contribute by stimulating growth factor pathways. It is thought that *H. pylori* infection leads to polyclonal B-cell proliferations and that eventually a monoclonal B-cell tumor (MALT lymphoma) emerges as a result of accumulation of mutations.



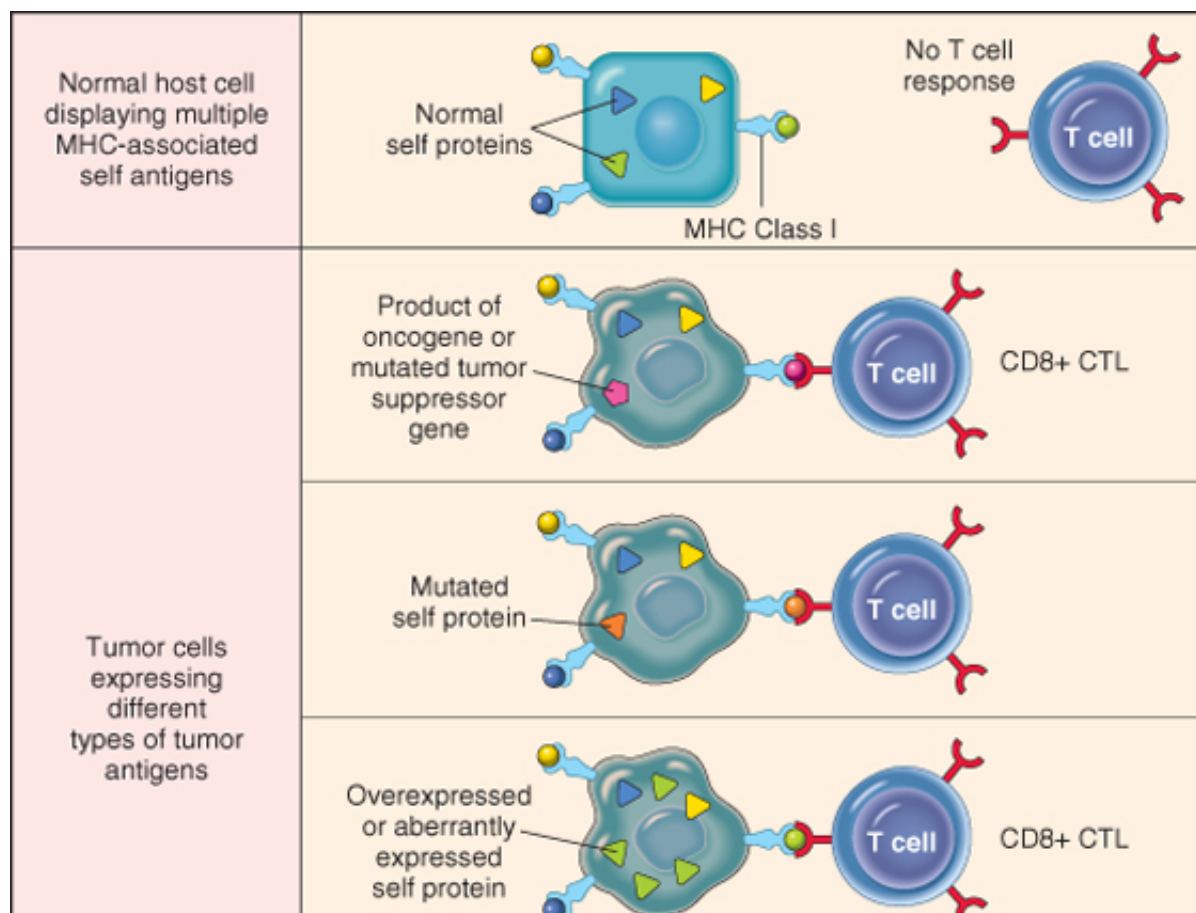
## HOST DEFENSE AGAINST TUMORS: TUMOR IMMUNITY

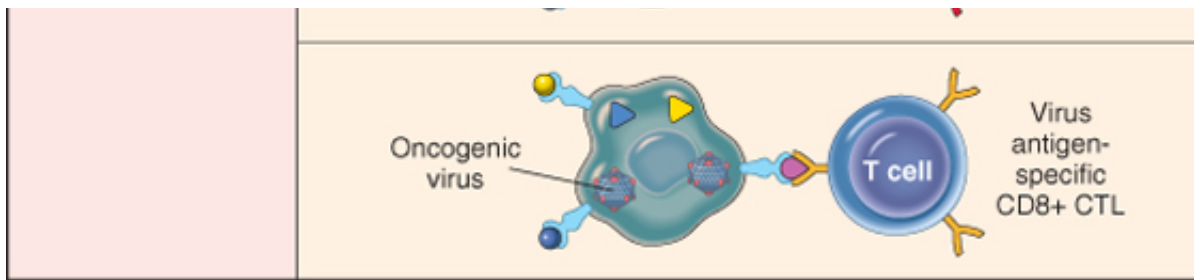
The idea that tumors are not entirely self was conceived by Ehrlich, who proposed that immune cells may be a "positive mechanism" capable of eliminating transformed cells. Subsequently, Lewis formalized this concept by coining the term *immune surveillance* to refer to recognition and destruction of tumor cells. The fact that cancers occur implies that immune surveillance is imperfect; however, that does not preclude the possibility that others may have been aborted. Here we address certain questions about tumor antigens: What host effector systems may recognize tumor cells? Is tumor immunity effective?

### Tumor Antigens

Antigens that elicit an immune response have been demonstrated in many experimentally induced tumors. Initially, they were broadly classified into two categories based on their patterns of expression: *tumor-specific antigens*, which are expressed only on tumor cells and not on any normal cells, and *tumor-associated antigens*, which are present on both tumor and normal cells. This classification, however, is imperfect, because many antigens thought to be tumor-specific are also expressed on normal cells as well. The modern classification of tumor antigens is based on their molecular structure. One of the major developments in the field of tumor immunology was the development of techniques for identifying tumor antigens that are recognized by cytotoxic lymphocytes (CTLs), because CTLs are the major immune defense mechanism against tumors. For example, tumor antigens can be derived from cytoplasmic proteins that are displayed bound to class I major histocompatibility complex (MHC) molecules. Below we describe the main classes of tumor antigens (Fig. 6-33).

#### Products of Mutated Oncogenes and Tumor Suppressor Genes





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Figure 6-33 Tumor antigens recognized by CD8+ T cells. (Modified from Abbas AK, Lichtman AH: Cellular and M  
Saunders, 2003.)

Neoplastic transformation, as we have discussed, results from genetic alterations, some of which surface antigens that are seen as non-self by the immune system. Antigens in this category are d cancer suppressor proteins. Unique tumor antigens arise from products of  $\beta$ -catenin, RAS, p53, a mutated in tumors. Because the mutant proteins are present only in tumors, their peptides are exp tumors may carry the same mutation, such antigens are shared by different tumors. Although CTL they do not appear to elicit protective responses in vivo.

#### *Products of Other Mutated Genes*

Because of the genetic instability of tumor cells, many genes are mutated in these cells, including the transformed phenotype and have no known function. Products of these mutated genes are po are extremely diverse, because the carcinogens that induce the tumors may randomly mutagenize proteins are found more frequently in chemical carcinogen- or radiation-induced animal tumors th can be targeted by the immune system, since there is no self-tolerance against them.

#### *Overexpressed or Aberrantly Expressed Cellular Proteins*

Tumor antigens may be normal cellular proteins that are abnormally expressed in tumor cells and human melanomas some tumor antigens are structurally normal proteins that are produced at low in tumor cells. One such antigen is tyrosinase, an enzyme involved in melanin biosynthesis that is and melanomas. T cells from melanoma patients recognize peptides derived from tyrosinase, rais vaccines may stimulate such responses to melanomas; clinical trials with these vaccines are ong patients are able to respond to a normal self-antigen. The probable explanation is that tyrosinase amounts and in so few cells that it is not recognized by the immune system and fails to induce tol

Another group, the so called "cancer-testis" antigens, are encoded by genes that are silent in all a name. Although the protein is present in the testis it is not expressed on the cell surface in an anti express MHC class I antigens. Thus, for all practical purposes, these antigens are tumor specific. family of genes. Although they are tumor specific, MAGE antigens are not unique for individual tur melanomas and a variable number of lung, liver, stomach, and esophageal carcinomas. Similar a have been detected in other tumors.

#### *Tumor Antigens Produced by Oncogenic Viruses*

As we have discussed, some viruses are associated with cancers. Not surprisingly, these viruses foreign by the immune system. The most potent of these antigens are proteins produced by latent include HPV and EBV. There is abundant evidence that CTLs recognize antigens of these viruses plays a role in surveillance against virus-induced tumors because of its ability to recognize and kil against HPV antigens have been found effective in prevention of cervical cancers in young female

#### *Oncofetal Antigens*

Oncofetal antigens or embryonic antigens, such as carcinoembryonic antigen (CEA) and  $\alpha$ -fetop embryogenesis but not in normal adult tissues. Derepression of the genes that encode these anti and liver cancers. Antibodies can be raised against these, and they are useful for detection of onc

and liver cancers. Antibodies can be raised against these, and they are useful for detection of one or another, but they are not entirely tumor specific, they can serve as serum markers for cancer.

#### *Altered Cell Surface Glycolipids and Glycoproteins*

Most human and experimental tumors express higher than normal levels and/or abnormal forms of which may be diagnostic markers and targets for therapy. These altered molecules include gangliosides and mucins. Although most of the epitopes recognized by antibodies raised against such antigens are not unique, they are present at higher levels on cancer cells than on normal cells. This class of antigens is a target for antibodies.

Several mucins are of special interest and have been the focus of diagnostic and therapeutic studies. MUC-1, expressed on ovarian carcinomas, and MUC-1, expressed on breast carcinomas. Unlike many other membrane proteins that are normally expressed only on the apical surface of breast ductal epithelium, MUC-1 is expressed on the entire surface of the tumor cell. In ductal carcinomas of the breast, however, the molecule is expressed in a new, tumor-specific carbohydrate and peptide epitopes. These epitopes induce both antibody and cell-mediated immunity and are therefore being considered as candidates for tumor vaccines.

#### *Cell Type-Specific Differentiation Antigens*

Tumors express molecules that are normally present on the cells of origin. These antigens are called differentiation antigens and are specific for particular lineages or differentiation stages of various cell types. Their importance lies in identifying the tissue of origin of tumors. For example, lymphomas may be diagnosed as B-cell or T-cell lymphomas by the presence of surface markers characteristic of this lineage, such as CD10 and CD20. Antibodies against these antigens are used in immunotherapy. These differentiation antigens are typically normal self-antigens, and therefore they are not immunogenic in tumor-bearing hosts.

### **Antitumor Effector Mechanisms**

Cell-mediated immunity is the dominant anti-tumor mechanism in vivo. Although antibodies can be shown to have a protective role under physiologic conditions. The cellular effectors that are involved in anti-tumor immunity are discussed in [Chapter 5](#), so it is necessary here only to characterize them briefly.

#### *Cytotoxic T Lymphocytes*

The role of specifically sensitized CTLs in experimentally induced tumors is well established. In humans, the role, chiefly against virus-associated neoplasms (e.g., EBV-induced Burkitt lymphoma and HPV-induced cervical carcinoma), suggests that the role of CD8<sup>+</sup> cells that can kill autologous tumor cells within human tumors suggests that the role of CD8<sup>+</sup> cells may be broader than previously suspected. In some cases, such CD8<sup>+</sup> T cells do not develop spontaneously but are generated by immunization with tumor antigen-pulsed dendritic cells.

#### *Natural Killer Cells*

NK cells are lymphocytes that are capable of destroying tumor cells without prior sensitization; they are cytotoxic against tumor cells. After activation with IL-2, NK cells can lyse a wide range of human tumors, including those that are nonimmunogenic for T cells. T cells and NK cells seem to provide complementary antitumor mechanisms. T cells recognize class I antigens cannot be recognized by T cells, but these tumors may trigger NK cells because they lack normal autologous class I molecules ([Chapter 5](#)). The triggering receptors on NK cells are extremely diverse. NKG2D proteins expressed on NK cells and some T cells are important activating receptors. These receptors recognize antigens that are expressed on tumor cells and cells that have incurred DNA damage and are at risk of becoming tumorigenic.

#### *Macrophages*

Activated macrophages exhibit cytotoxicity against tumor cells in vitro. T cells, NK cells, and macrophages all have cytotoxic activity, because interferon- $\gamma$ , a cytokine secreted by T cells and NK cells, is a potent activator of macrophages. Macrophages may kill tumors by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen species and secretion of tumor necrosis factor (TNF)).

#### *Humoral Mechanisms*

Although there is no evidence for the protective effects of anti-tumor antibodies against spontaneous tumors, there is evidence for the protective effects of anti-tumor antibodies against experimentally induced tumors. In some cases, antibodies can be shown to have a protective role under physiologic conditions.



antibodies against tumor cells can be therapeutically effective. A monoclonal antibody against CD20 is used for treatment of certain non-Hodgkin lymphomas.

## Immune Surveillance

Given the host of possible and potential antitumor mechanisms, is there any evidence that they occur in the absence of neoplasms? The strongest argument for the existence of immune surveillance is the increased frequency of cancers in immunodeficient hosts. About 5% of individuals with congenital immunodeficiencies develop cancers, a rate that is much higher than in the general population without such immunodeficiencies. Analogously, immunosuppressed transplant recipients and patients with AIDS have increased numbers of malignancies. It should be noted that most (but not all) of the lymphomas of activated B cells. Particularly illustrative is X-linked lymphoproliferative disorder. With Epstein-Barr virus infection, such infection does not take the usual self-limited form of infectious mononucleosis but instead takes a sometimes fatal form of infectious mononucleosis or, even worse, malignant lymphoma.

Most cancers occur in individuals who do not suffer from any overt immunodeficiency. If immune surveillance is the immune system in immunocompetent hosts? Several escape mechanisms have been proposed.

*Selective outgrowth of antigen-negative variants.* During tumor progression, strongly immunoreactive variants are often eliminated. *Loss or reduced expression of histocompatibility molecules.* Tumor cells may fail to express MHC class I molecules, thus escaping attack by CTLs. Such cells, however, may trigger NK cells. *Immunosuppression.* Tumor cells (by secreting immunosuppressive factors and ionizing radiation) suppress host immune responses. Tumors or tumor products also may suppress immune responses. TGF- $\beta$ , secreted in large quantities by many tumors, is a potent immunosuppressant. In some cases, the tumor may inhibit tumor immunity. Several mechanisms of such inhibition have been proposed. Tumor cells may lead to engagement of the T-cell inhibitory receptor, CTLA-4, or activation of regulatory T cells, all of which suppress immune responses.

It is worth mentioning that although much of the focus in the field of tumor immunity has been on the immune system defending against tumors, there is some recent evidence that, paradoxically, the immune system can promote tumor growth. It is possible that activated lymphocytes and macrophages produce growth factors for tumor cells. Tumor necrosis factor (TNF), which enhances tumor invasion, may also be produced. Harnessing the protective actions of the immune system to increase tumor growth is obviously an important goal of immunologists and oncologists.

## SUMMARY

### Immune Surveillance

Tumor cells can be recognized by the immune system as non-self and destroyed by immune cells. This process is mediated by predominantly cell-mediated mechanisms. Tumor antigens are presented on the cell surface by MHC class I molecules and are recognized by CD8<sup>+</sup> CTLs. The antigens include products of mutated proto-oncogenes, tumor suppressor gene products, aberrantly expressed proteins, tumor antigens produced by oncogenic virus, altered glycolipids and glycoproteins, and cell type-specific differentiation antigens. Immunosuppressed patients have an increased risk of cancer. In some cases, tumor cells may avoid the immune system by several mechanisms, including selection of antigen-negative variants, loss or reduced expression of histocompatibility molecules, and immunosuppression mediated by secretion of factors (e.g., TGF- $\beta$ ) from the tumor.





## CLINICAL ASPECTS OF NEOPLASIA

Ultimately the importance of neoplasms lies in their effects on patients. Although malignant tumors are of course more threatening than benign tumors, any tumor, even a benign one, may cause morbidity and mortality. Indeed, both malignant and benign tumors may cause problems because of (1) location and impingement on adjacent structures, (2) functional activity such as hormone synthesis or the development of paraneoplastic syndromes, (3) bleeding and infections when the tumor ulcerates through adjacent surfaces, (4) symptoms that result from rupture or infarction, and (5) cachexia or wasting. The following discussion considers the effects of a tumor on the host, the grading and clinical staging of cancer, and the laboratory diagnosis of neoplasms.

### Effects of Tumor on Host

Location is crucial in both benign and malignant tumors. A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland and give rise to hypopituitarism. A 0.5-cm leiomyoma in the wall of the renal artery may lead to renal ischemia and serious hypertension. A comparably small carcinoma within the common bile duct may induce fatal biliary tract obstruction.

Hormone production is seen with benign and malignant neoplasms arising in endocrine glands. Adenomas and carcinomas arising in the  $\beta$ -cells of the islets of the pancreas can produce hyperinsulinism, sometimes fatal. Analogously, some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia). Such hormonal activity is more likely with a well-differentiated benign tumor than with a corresponding carcinoma.

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A tumor may ulcerate through a surface, with consequent bleeding or secondary infection. Benign or malignant neoplasms that protrude into the gut lumen may become caught in the peristaltic pull of the gut, causing intussusception ([Chapter 15](#)) and intestinal obstruction or infarction.

### Cancer Cachexia

Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, referred to as *cachexia*. There is some correlation between the size and extent of spread of the cancer and the severity of the cachexia. However, cachexia is not caused by the nutritional demands of the tumor. Although patients with cancer are often anorexic, current evidence indicates that cachexia results from the action of soluble factors such as cytokines produced by the tumor and the host rather than reduced food intake. In patients with cancer, calorie expenditure remains high, and basal metabolic rate is increased, despite reduced food intake. This is in contrast to the lower metabolic rate that occurs as an adaptational response in starvation. The basis of these metabolic abnormalities is not fully understood. It is suspected that TNF produced by macrophages in response to tumor cells or by the tumor cells themselves mediates cachexia. TNF suppresses appetite and inhibits the action of lipoprotein lipase, inhibiting the release of free fatty acids from lipoproteins. Additionally, a protein-mobilizing factor called proteolysis-inducing factor, which causes breakdown of skeletal muscle proteins by the ubiquitin-proteasome pathway, has been detected in the serum of cancer patients. Other molecules with lipolytic action also have been found. There is no satisfactory treatment for cancer cachexia other than removal of the underlying cause, the tumor.

### Paraneoplastic Syndromes

### Paraneoplastic Syndromes

Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor are referred to as *paraneoplastic syndromes*. They appear in 10% to 15% of patients with cancer, and it is important to recognize them for several reasons:

They may represent the earliest manifestation of an occult neoplasm. In affected patients, they may represent significant clinical problems and may even be lethal. They may mimic metastatic disease and confound treatment.

The paraneoplastic syndromes are diverse and are associated with many different tumors (Table 6-5). The most common syndromes are hypercalcemia, Cushing syndrome, and nonbacterial thrombotic endocarditis; the neoplasms most often associated with these and other syndromes are lung and breast cancers and hematologic malignancies. Hypercalcemia in cancer patients is multifactorial, but the most important mechanism is the synthesis of a parathyroid hormone-related protein (PTHrP) by tumor cells. Also implicated are other tumor-derived factors, such as TGF- $\alpha$ , a polypeptide factor that activates osteoclasts, and the active form of vitamin D. Another possible mechanism for hypercalcemia is widespread osteolytic metastatic disease of bone, but *it should be noted that hypercalcemia resulting from skeletal metastases is not a paraneoplastic syndrome*. Cushing syndrome as a paraneoplastic phenomenon is usually related to ectopic production of ACTH or ACTH-like polypeptides by cancer cells, as occurs in small-cell cancers of the lung. Sometimes one tumor induces several syndromes concurrently. For example, bronchogenic carcinomas may elaborate products identical to or having the effects of ACTH, antidiuretic hormone, parathyroid hormone, serotonin, human chorionic gonadotropin, and other bioactive substances.

Paraneoplastic syndromes may also manifest as hypercoagulability leading to venous thrombosis and nonbacterial thrombotic endocarditis (Chapter 11). Other manifestations are clubbing of the fingers and hypertrophic osteoarthropathy in patients with lung carcinomas (Chapter 13). Still others are discussed in the consideration of cancers of the various organs of the body.

### Grading and Staging of Cancer

Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary for making accurate prognosis and for comparing end results of various treatment protocols. For instance, the results of treating extremely small, highly differentiated thyroid adenocarcinomas that are localized to the thyroid gland are likely to be different from those obtained from treating highly anaplastic thyroid cancers that have invaded the neck organs.

The *grading* of a cancer attempts to establish some estimate of its aggressiveness or level of malignancy based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor. The cancer may be classified as grade I, II, III, or IV, in order of increasing anaplasia. Criteria for the individual grades vary with each form of neoplasia and so are not detailed here. Difficulties in establishing clear-cut criteria have led in some instances to descriptive characterizations (e.g., "well-differentiated adenocarcinoma with no evidence of vascular or lymphatic invasion" or "highly anaplastic sarcoma with extensive vascular invasion").

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Table 6-5. Paraneoplastic Syndromes

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanism
--------------------	----------------------------------	------------------

<b>Endocrinopathies</b>		
Cushing syndrome	Small-cell carcinoma of lung	ACTH or ACTH-like substance
	Pancreatic carcinoma	
	Neural tumors	
Syndrome of inappropriate antidiuretic hormone secretion	Small-cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung	Parathyroid hormone-related protein, TGF- $\alpha$ , TNF, IL-1
	Breast carcinoma	
	Renal carcinoma	
	Adult T-cell leukemia/lymphoma	
	Ovarian carcinoma	
Hypoglycemia	Fibrosarcoma	Insulin or insulin-like substance
	Other mesenchymal sarcomas	
	Hepatocellular carcinoma	
Carcinoid syndrome	Bronchial adenoma (carcinoid)	Serotonin, bradykinin
	Pancreatic carcinoma	
	Gastric carcinoma	
Polycythemia	Renal carcinoma	Erythropoietin
	Cerebellar hemangioma	
	Hepatocellular carcinoma	
<b>Nerve and Muscle Syndrome</b>		
Myasthenia	Bronchogenic carcinoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma	
<b>Dermatologic Disorders</b>		
Acanthosis nigricans	Gastric carcinoma	Immunologic; secretion of epidermal growth factor
	Lung carcinoma	
	Uterine carcinoma	
Dermatomyositis	Bronchogenic, breast carcinoma	Immunologic
<b>Osseous, Articular, and Soft-Tissue Changes</b>		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
<b>Vascular and Hematologic Changes</b>		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma	Tumor products (mucins that activate clotting)
	Other cancers	
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymic neoplasms	Unkown
<b>Others</b>		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

ACTH, adrenocorticotrophic hormone; TGF, transforming growth factor; TNF, tumor necrosis factor; IL, interleukin.

*Staging of cancers is based on the size of the primary lesion, its extent of spread to regional*



lymph nodes, and the presence or absence of metastases. This assessment is usually based on clinical and radiographic examination (computed tomography and magnetic resonance imaging) and in some cases surgical exploration. Two methods of staging are currently in use: the TNM system (*T*, primary tumor; *N*, regional lymph node involvement; *M*, metastases) and the AJC (American Joint Committee) system. In the TNM system, T1, T2, T3, and T4 describe the increasing size of the primary lesion; N0, N1, N2, and N3 indicate progressively advancing node involvement; and M0 and M1 reflect the absence or presence of distant metastases. In the AJC method, the cancers are divided into stages 0 to IV, incorporating the size of primary lesions and the presence of nodal spread and of distant metastases. Examples of the application of these two staging systems are cited in subsequent chapters. It is worth noting that *when compared with grading, staging has proved to be of greater clinical value.*

## SUMMARY

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### Clinical Aspects of Tumors

Cachexia, defined by progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, is caused by release of cytokines by the tumor or host. Paraneoplastic syndromes, defined by systemic symptoms that cannot be explained by tumor spread or by hormones appropriate to the tissue, are caused by the ectopic production and secretion of bioactive substances, such as ACTH, PTHrP, or TGF- $\alpha$ . Grading of tumors is determined by cytologic appearance and is based on the idea that behavior and differentiation are related, with poorly differentiated tumors having more aggressive behavior. Staging, determined by surgical exploration or imaging, is based on size, local and regional lymph node spread, and distant metastases. Staging has greater clinical value than grading.

## Laboratory Diagnosis of Cancer

### Morphologic Methods

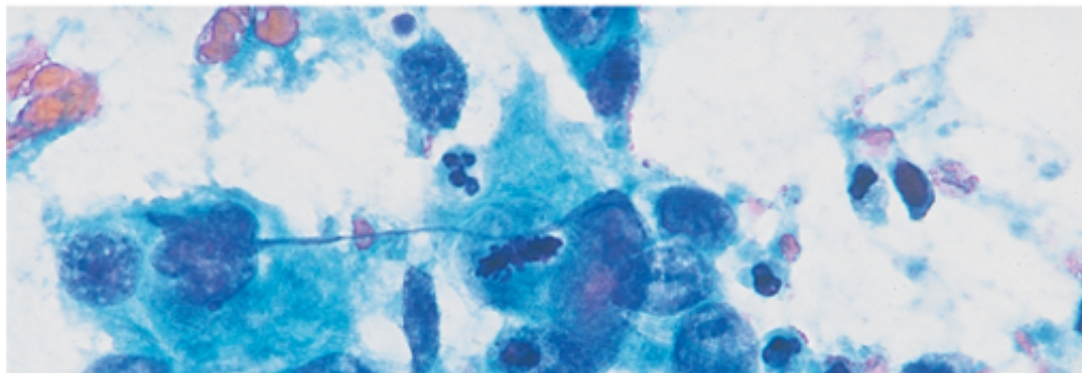
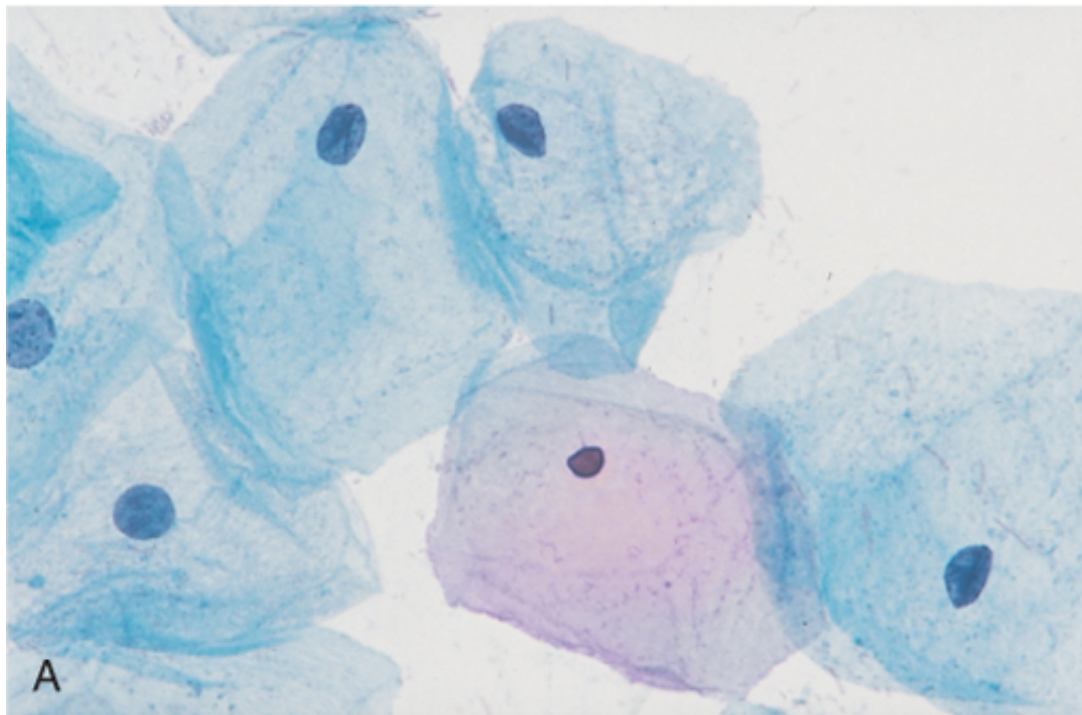
In most instances, the laboratory diagnosis of cancer is not difficult. The two ends of the benign-malignant spectrum pose no problems; however, in the middle lies a "no man's land" where the wise tread cautiously. Clinicians tend to underestimate the contributions they make to the diagnosis of a neoplasm. Clinical data are invaluable for optimal pathologic diagnosis. Radiation-induced changes in the skin or mucosa can be similar to those of cancer. Sections taken from a healing fracture can mimic an osteosarcoma. The laboratory evaluation of a lesion can be only as good as the specimen submitted for examination. The specimen must be adequate, representative, and properly preserved.

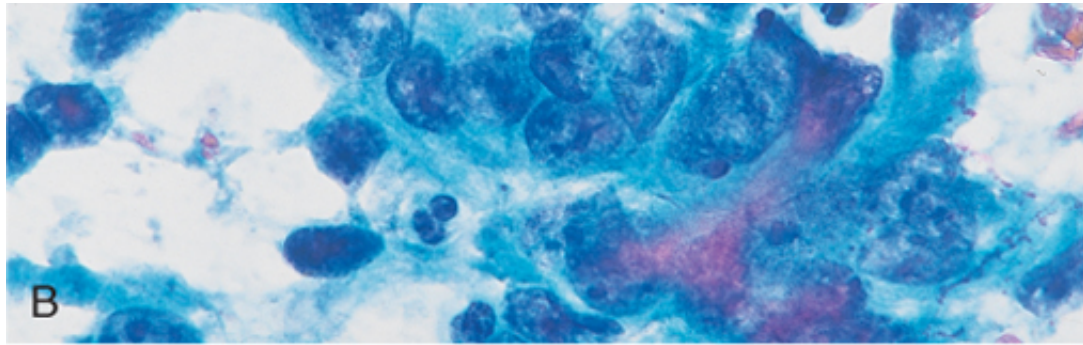
Several sampling approaches are available, including excision or biopsy, fine-needle aspiration, and cytologic smears. When excision of a lesion is not possible, selection of an appropriate site for biopsy of a large mass requires awareness that the margins may not be representative and the center may be largely necrotic. Analogously with disseminated lymphoma (i.e., involving many nodes), nodes in the inguinal region that drain large areas of the body often undergo reactive changes that may mask neoplastic involvement. Requesting *frozen-section* diagnosis is sometimes desirable, as, for example, in determining the nature of a mass lesion or in evaluating the regional lymph nodes in a patient with cancer for metastasis. This method, in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes. In experienced, competent hands, frozen-section diagnosis is accurate, but there are particular instances in which the better histologic detail provided by the more time-consuming routine methods is needed. In such instances, it is better to wait a few

more time-consuming routine methods is needed. In such instances, it is better to wait a few days, despite the drawbacks, than to perform inadequate or unnecessary surgery.

*Fine-needle aspiration* of tumors is another approach that is widely used. It involves aspiration of cells from a mass, followed by cytologic examination of the smear. This procedure is used most commonly with readily palpable lesions affecting the breast, thyroid, lymph nodes, and salivary glands. Modern imaging techniques permit extension of the method to deeper structures, such as the liver, pancreas, and pelvic lymph nodes. It obviates surgery and its attendant risks. Although it entails some difficulties, such as small sample size and sampling errors, in experienced hands it can be extremely reliable, rapid, and useful.

*Cytologic (Papanicolaou) smears* provide another method for the detection of cancer. Historically, this approach has been used widely for the discovery of carcinoma of the cervix, often at an in situ stage, but now it is used with many other forms of suspected malignancy, such as endometrial carcinoma, bronchogenic carcinoma, bladder and prostate tumors, and gastric carcinomas; for the identification of tumor cells in abdominal, pleural, joint, and cerebrospinal fluids; and, less commonly, with other forms of neoplasia. Neoplastic cells are less cohesive than others and so are shed into fluids or secretions (Fig. 6-34). The shed cells are evaluated for features of anaplasia indicative of their origin from a tumor. The gratifying control of cervical cancer is the best testament to the value of the cytologic method.





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 Figure 6-34 **A**, Normal Papanicolaou smear from the uterine cervix. Large, flat cells with small nuclei. **B**, Abnormal smear containing a sheet of malignant cells with large hyperchromatic nuclei. There is nuclear pleomorphism, and one cell is in mitosis. There are few interspersed neutrophils with compact lobated nuclei and much smaller size. (Courtesy of Dr. Richard M. DeMay, Department of Pathology, University of Chicago, Chicago, Illinois.)

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*Immunocytochemistry* offers a powerful adjunct to routine histology. Detection of cytokeratin by specific monoclonal antibodies labeled with peroxidase points to a diagnosis of undifferentiated carcinoma rather than large-cell lymphoma. Similarly, detection of prostate-specific antigen (PSA) in metastatic deposits by immunohistochemistry allows definitive diagnosis of a primary tumor in the prostate. Immunocytochemical detection of estrogen receptors allows prognostication and directs therapeutic intervention in breast cancers.

*Flow cytometry* is used routinely in the classification of leukemias and lymphomas. In this method, fluorescent antibodies against cell surface molecules and differentiation antigens are used to obtain the phenotype of malignant cells.

### **Tumor Markers**

Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood cannot be utilized for definitive diagnosis of cancer; however, they contribute to finding cases and in some instances are useful in determining the effectiveness of therapy or the appearance of a recurrence. The application of these assays is considered with many of the specific forms of neoplasia discussed in other chapters, so only a few examples suffice here. PSA, used to screen for prostatic adenocarcinoma, may be one of the most used, and most successful, tumor markers in clinical practice. Prostatic carcinoma can be suspected when elevated levels of PSA are found in the blood. However, PSA screening also highlights problems encountered by virtually every tumor marker. Although PSA levels are often elevated in cancer, PSA levels also may be elevated in benign prostatic hyperplasia ([Chapter 18](#)). Furthermore, there is no PSA level that ensures that a patient does not have prostate cancer. *Thus, the PSA test suffers from both low sensitivity and low specificity.* Other tumor markers occasionally used in clinical practice include carcinoembryonic antigen (CEA), which is elaborated by carcinomas of the colon, pancreas, stomach, and breast, and  $\alpha$ -fetoprotein, which is produced by hepatocellular carcinomas, yolk sac remnants in the gonads, and occasionally teratocarcinomas and embryonal cell carcinomas. Unfortunately, like PSA, both of these markers can be produced by a variety of non-neoplastic conditions as well. Thus, CEA and  $\alpha$ -fetoprotein assays lack both specificity and sensitivity required for the early detection of cancers. They are still particularly useful in the detection of recurrences after excision. With successful resection of the tumor, these markers disappear from the serum; their reappearance almost always signifies the beginning of the end. CEA is further discussed in [Chapter 15](#) and  $\alpha$ -fetoprotein in [Chapter 16](#).

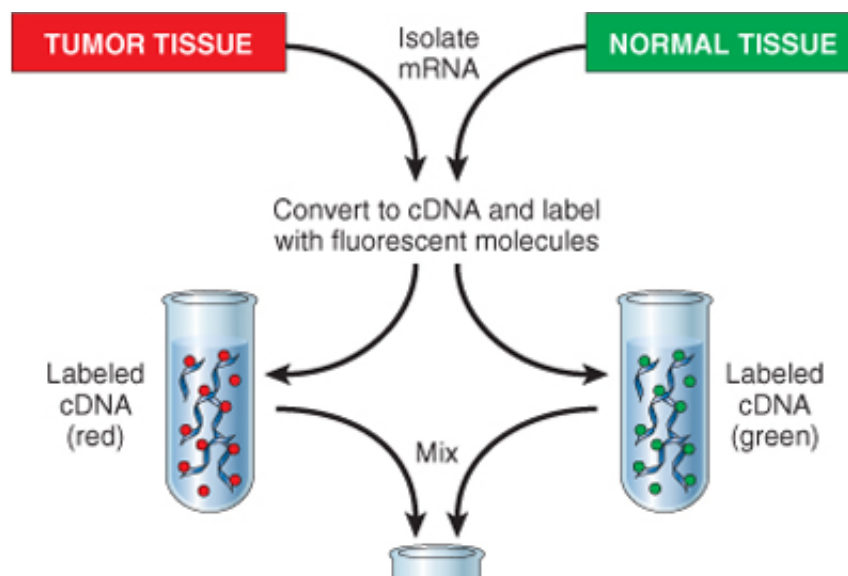
### **Molecular Diagnosis**

An increasing number of molecular techniques are being used for the diagnosis of tumors and for predicting their behavior.

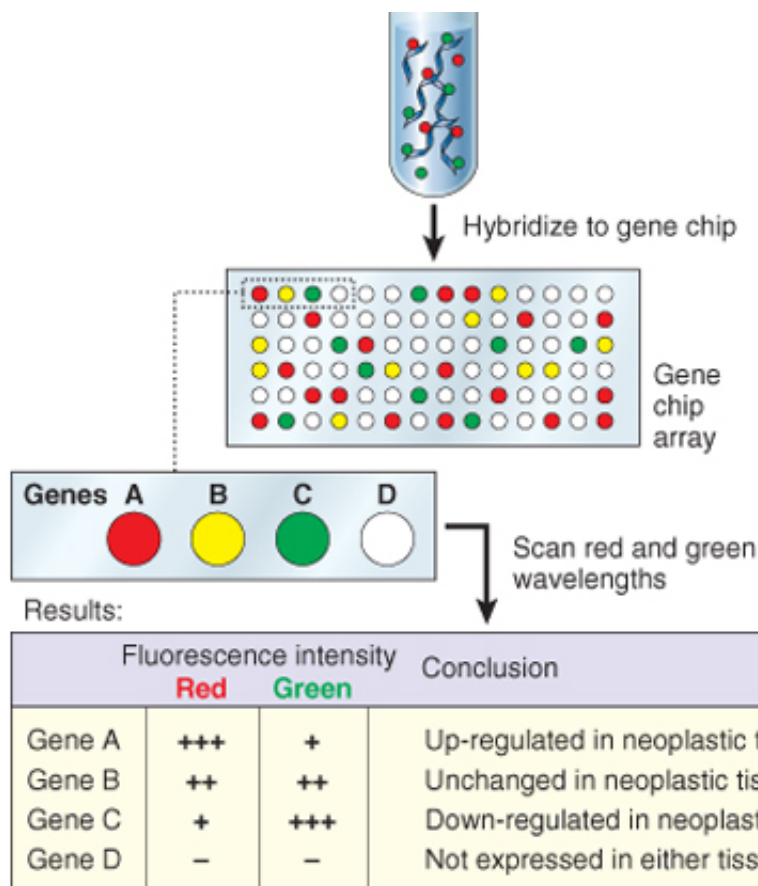
1. **Diagnosis of malignancy.** Because each T and B cell has unique rearrangement of its antigen receptor genes, polymerase chain reaction (PCR)-based detection of T-cell receptor or immunoglobulin genes allows distinction between monoclonal (neoplastic) and polyclonal (reactive) proliferations. Many hematopoietic neoplasms, and a few solid tumors, are defined by particular translocations, and thus the diagnosis can be made by detection of such translocations. For example, fluorescence in situ hybridization (FISH) or PCR ([Chapter 7](#)) can be used to detect translocations characteristic of Ewing sarcoma and several leukemias and lymphomas. PCR-based detection of *BCR-ABL* transcripts provides the molecular diagnosis of chronic myeloid leukemia.
2. **Prognosis and behavior.** Certain genetic alterations are associated with a poor prognosis, and thus the presence of these alterations determines the patient's subsequent therapy. FISH and PCR methods can be used to detect amplification of oncogenes such as *HER-2/NEU* and *N-MYC*, which provide prognostic and therapeutic information for breast cancers and neuroblastomas.
3. **Detection of minimal residual disease.** Another emerging use of molecular techniques is detection of minimal residual disease after treatment. For example, detection of *BCR-ABL* transcripts by PCR gives a measure of residual disease, in patients treated for chronic myeloid leukemia.
4. **Diagnosis of hereditary predisposition to cancer.** Germ-line mutation of several tumor suppressor genes, such as *BRCA1*, increases a patient's risk of developing certain types of cancer. Thus, detection of these mutated alleles may allow the patient and physician to devise an aggressive screening protocol, as well as to consider prophylactic surgery. In addition, such detection allows genetic counseling of relatives at risk.

### **Molecular Profiling of Tumors**

One of the most exciting advances in the molecular analysis of tumors has been made possible by DNA-microarray analysis. This technique allows simultaneous measurements of the expression levels of several thousand genes. The principle of this so-called gene chip technology is illustrated in [Figure 6-35](#) and described briefly here.







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 Figure 6-35 Schematic illustration of cDNA microarray analysis. mRNA is extracted from the samples, reverse transcribed to cDNA, and labeled with fluorescent molecules. In the case illustrated, *red* fluorescent molecules were used for normal cDNA, and *green* molecules were used for tumor cDNA. The labeled cDNAs are mixed and applied to a gene chip, which contains thousands of DNA probes representing known genes. The labeled cDNAs hybridize to spots that contain complementary sequences. The hybridization is detected by laser scanning of the chip, and the results are read in units of red or green fluorescence intensity. In the example shown, spot A has high red fluorescence, indicating that a greater number of cDNAs from neoplastic cells hybridized to gene A. Thus, gene A seems to be up-regulated in tumor cells. (Courtesy of Dr. Robert Anders, Department of Pathology, University of Chicago, Chicago, Illinois.)

As can be seen, the process begins by extraction of mRNA from any two sources (e.g., normal and malignant, normal and preneoplastic, or two tumors of the same histologic type). cDNA copies of the mRNA are synthesized *in vitro* with fluorescently labeled nucleotides. The fluorescence-labeled cDNA strands are hybridized to sequence-specific DNA probes linked to a solid support, such as a silicon chip. A 1-cm<sup>2</sup> chip can contain thousands of probes arranged in an array of columns and rows. After hybridization, high-resolution laser scanning detects fluorescent signals from each of the spots. The fluorescence intensity of each spot is proportional to the level of expression of the original mRNA used to synthesize the cDNA hybridized to that spot. For each sample, therefore, the expression level of thousands of genes is obtained, and by using bioinformatic tools, the relative levels of gene expression in different samples can be compared. In essence, a molecular profile is generated for each tissue analyzed.

Such analysis has revealed that phenotypically identical large B-cell lymphomas (Chapter 12) from different patients are heterogeneous with respect to their gene expression. Nevertheless, clusters of gene expression patterns can be detected that allow segregation of phenotypically similar tumors into distinct subcategories with dramatically different survival rates. This type of molecular profiling indicates that the currently available morphologic and molecular tools are

insufficient for stratification of tumors into prognostically different subgroups. Similar analyses have been performed on breast cancers and melanomas. Although the data currently available have to be validated by prospective analysis of a larger cohort of patients, the proof of principle has been obtained. It is likely that, in the near future, molecular profiling will become an adjunct in the diagnosis, classification, and management of cancer. This type of analysis may also reveal novel gene targets for development of new drugs. Thus, therapy may be tailored to the specific genes dysregulated in a given tumor. Who knows, advertisements for "designer genes" may appear side by side with ads for "designer jeans"!

## SUMMARY

### Laboratory Diagnosis of Cancer

Several sampling approaches exist for the diagnosis of tumors, including excision, biopsy, fine-needle aspiration, and cytologic smears. Immunohistochemistry and flow cytometry help in the diagnosis and classification of tumors, because distinct protein expression patterns define different entities. Proteins released by tumors into the serum, such as PSA, can be used to screen populations for cancer and to monitor recurrence following treatment. Molecular analyses are used to determine diagnosis, prognosis, the detection of minimal residual disease, and the diagnosis of hereditary predisposition to cancer. Molecular profiling of tumors by cDNA arrays can determine expression of large segments of the genome at once and can be useful in molecular stratification of otherwise identical tumors for the purpose of treatment and prognostication.

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## 7 Genetic and Pediatric Diseases

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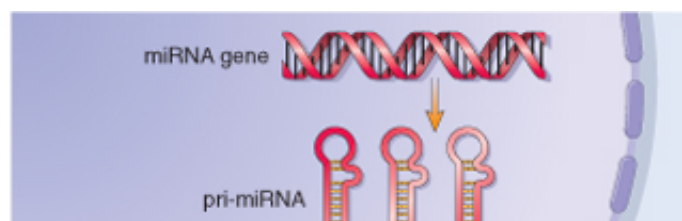
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### GENETIC DISEASES

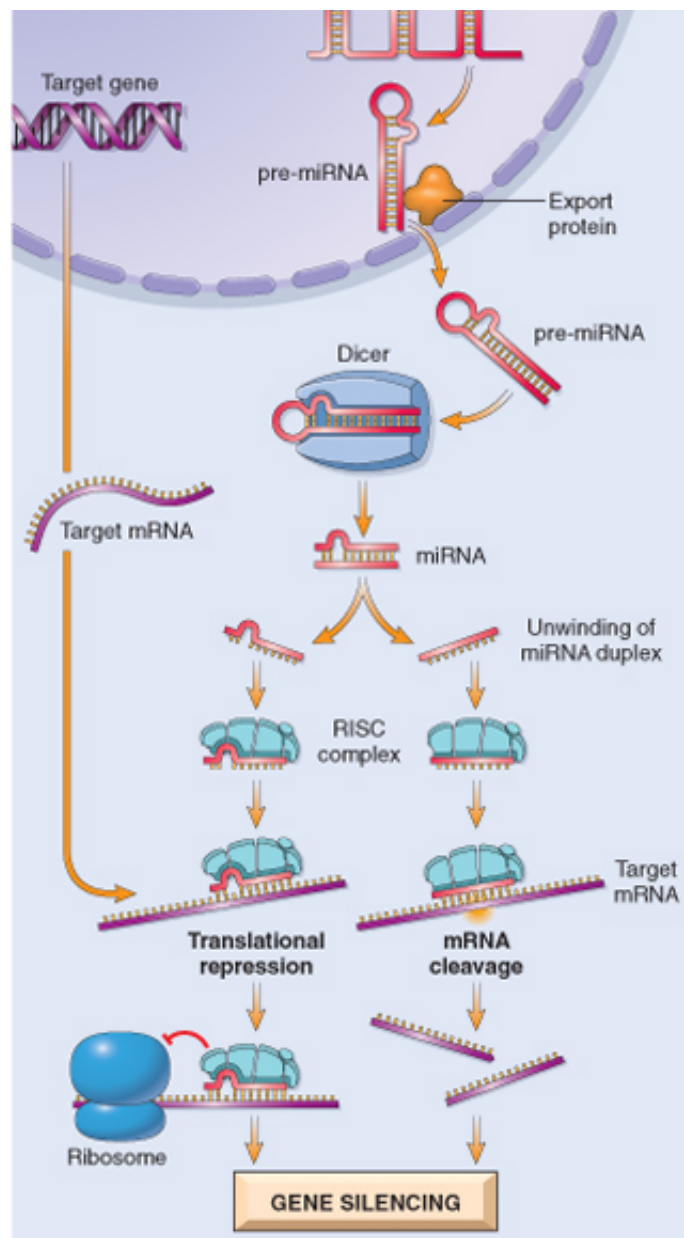
The completion of the human genome project has been a landmark event in the study of human diseases. We now know that humans have only about 30,000 genes, far fewer than the 100,000 previously estimated. The unraveling of our "genetic architecture" promises to unlock secrets of inherited as well as acquired human disease, since ultimately all diseases involve changes in gene structure or expression. Powerful technologies now allow applications of the human gene sequences to the analysis of human diseases. For example, DNA and RNA microarrays ("gene chips") can be used to simultaneously screen for the expression of thousands of genes in diseased tissues. Such "molecular profiling" has become an important tool in the study of malignant diseases ([Chapter 6](#)).

It is worth noting that until recently the major focus of gene hunting has been discovery of structural genes whose products encode proteins. Recent studies indicate, however, that a very large number of genes do not encode proteins. Instead, their products play important regulatory functions. The most recent among this class are genes that encode small RNA molecules, so-called microRNAs (miRNAs). miRNAs, unlike other RNAs, do not encode proteins but instead inhibit gene expression. Silencing of gene expression by miRNA is preserved in all living forms from plants to humans and therefore must be a fundamental mechanism of gene regulation. Because of their profound influence on gene regulation, miRNAs are assuming central importance in understanding normal developmental pathways, as well as pathologic conditions, such as cancer. Such is the importance of the discovery of gene silencing by miRNAs that Andrew Fire and Craig Mello were awarded the Nobel prize in physiology or medicine in 2006, a mere eight years after they published their work in 1998.

By current estimates, there are approximately 1000 genes in humans that encode miRNAs, accounting for about 3% of the human genome. Transcription of miRNA genes produces primary microRNA transcript (pri-miRNA), which is processed within the nucleus to form another structure, called pre-miRNA ([Fig. 7-1](#)). With the help of specific transporter proteins, pre-miRNA is exported to the cytoplasm. Additional "cutting" by an enzyme, appropriately called Dicer, generates mature miRNAs that are about 21 to 30 nucleotides in length (hence the name "micro"). At this stage the miRNA is still double-stranded. Next, the miRNA unwinds, and single strands of this duplex are incorporated into a multiprotein complex called RNA-induced silencing complex (RISC). Base pairing between the miRNA strand and its target mRNA directs the RISC to either cause mRNA cleavage or repress its translation. In this way, the gene from which the target mRNA was derived is silenced (at a post-transcriptional state). Given that the numbers of miRNA genes are far fewer than those that encode proteins, it follows that a given miRNA can silence many target genes. The precise mechanism by which the target specificity of miRNA is determined remains to be fully elucidated.







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 Figure 7-1 Generation of micro RNAs and their mode of action in regulating gene function. Pri-miRNA, primary microRNA transcript; Pre-miRNA, precursor microRNA; RISC, RNA-induced silencing complex.

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Another species of gene-silencing RNA, called small interfering RNAs (siRNAs), works in a manner quite similar to that of miRNA. Unlike miRNA, however, siRNA precursors are introduced by investigators into the cell. Their processing by Dicer and functioning via RISC are essentially similar to that described for miRNA. siRNAs are becoming powerful tools for studying gene function and may in the future be used therapeutically to silence specific genes, such as oncogenes, whose products are involved in neoplastic transformation.

With this background of developments in human genetics, we can turn to the time-honored classification of human diseases into three categories: (1) those that are genetically determined, (2) those that are almost entirely environmentally determined, and (3) those to which both nature and nurture contribute. However, progress in understanding the molecular

basis of many so-called environmental disorders has tended to blur these distinctions. At one time, microbial infections were cited as examples of disorders arising wholly from environmental influences, but it is now clear that to a considerable extent, an individual's genetic makeup influences his or her immune response and susceptibility to microbiologic infections. Despite the complexities of this nature-nurture interplay, there is little doubt that nature (i.e., the genetic component) plays a major, if not the determining, role in the occurrence and severity of many human diseases. In fact, the genetic contribution even in common diseases is far greater than is commonly appreciated.

Surveys indicate that as many as 20% of the pediatric inpatients in university hospitals suffer from disorders of genetic origin. These data describe only the tip of the iceberg. Chromosomal aberrations have been identified in as many as 50% of spontaneous abortuses during the first trimester, and many more abortuses probably had gene mutations. Only those mutations compatible with independent existence constitute the reservoir of genetic disease in the population at large.

Because several pediatric disorders are of genetic origin, we discuss developmental and pediatric diseases along with genetic diseases in this chapter. However, *it must be borne in mind that not all genetic disorders present in infancy and childhood, and conversely, many pediatric diseases are not of genetic origin.* To the latter category belong diseases resulting from immaturity of organ systems. In this context it is helpful to clarify three commonly used terms: hereditary, familial, and congenital. *Hereditary* disorders, by definition, are derived from one's parents, are transmitted in the gametes through the generations, and therefore are *familial*. The term *congenital* simply implies "present at birth." It should be noted that some congenital diseases are not genetic (e.g., congenital syphilis). On the other hand, not all genetic diseases are congenital; the expression of Huntington disease, for example, begins only after the third or fourth decade of life.

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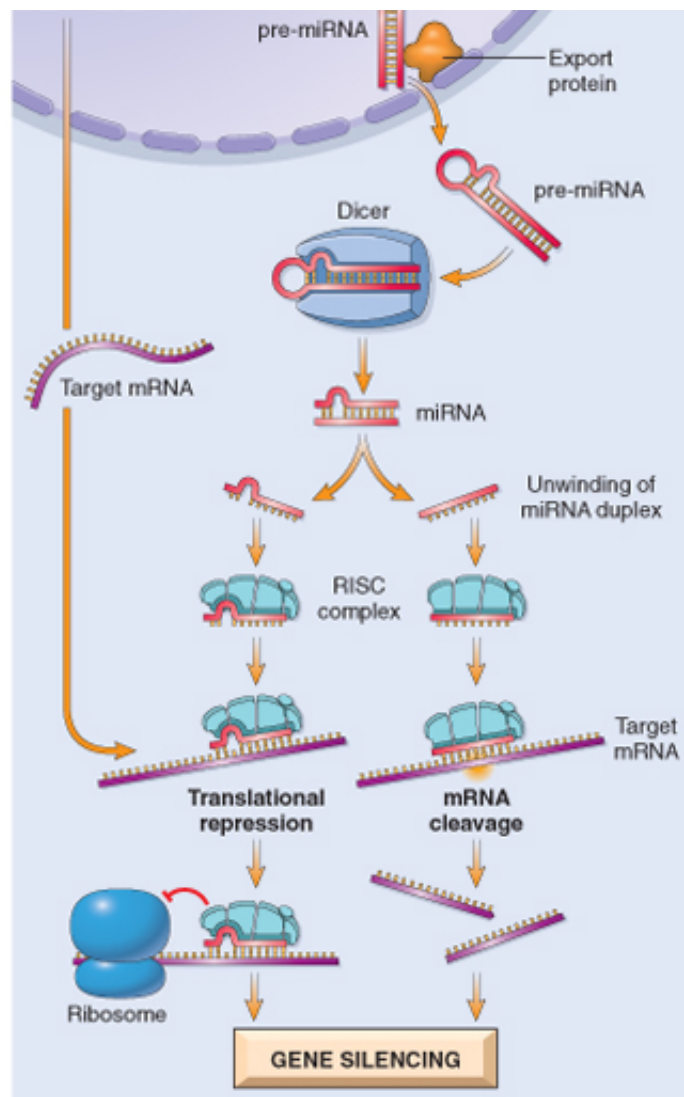
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It is beyond the scope of this book to review normal human genetics, but it is beneficial to recall some fundamental concepts that have a bearing on the understanding of genetic diseases.





## MUTATIONS

As is well known, the term *mutation* refers to permanent changes in the DNA. Those that affect germ cells are transmitted to the progeny and may give rise to inherited diseases. Mutations in somatic cells are not transmitted to the progeny but are important in the causation of cancers and some congenital malformations.

Details of specific mutations and their effects are discussed along with the relevant disorders throughout this text. Here we cite only some common examples of gene mutations and their effects.

*Point mutations* result from the substitution of a single nucleotide base by a different base, resulting in the replacement of one amino acid by another in the protein product. The mutation giving rise to sickle cell anemia is an excellent example of a point mutation that alters the meaning of the genetic code. Such mutations are sometimes called *missense mutations*.

In contrast, certain point mutations may change an amino acid codon to a chain termination codon, or *stop codon*. Such "nonsense" mutations interrupt translation, and the resultant truncated proteins are rapidly degraded.

*Frameshift mutations* occur when the insertion or deletion of one or two base pairs alters the reading frame of the DNA strand.

*Trinucleotide repeat mutations* belong to a special category, because these mutations are characterized by amplification of a sequence of 3 nucleotides. Although the specific nucleotide sequence that undergoes amplification differs in various disorders, all affected sequences share the nucleotides guanine (G) and cytosine (C). For example, in fragile X syndrome, prototypical of this category of disorders, there are 200 to 4000 tandem repeats of the sequence CGG within a gene called *FMR1*. In normal populations, the number of repeats is small, averaging 29. The expansions of the trinucleotide sequences prevent normal expression of the *FMR1* gene, thus giving rise to mental retardation. Another distinguishing feature of trinucleotide repeat mutations is that they are dynamic (i.e., the degree of amplification increases during gametogenesis). These features, discussed in greater detail later in this chapter, influence the pattern of inheritance and the phenotypic manifestations of the diseases caused by this class of mutations.

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With this brief review of the nature of mutations, we can turn our attention to the three major categories of genetic disorders: (1) those related to mutant genes of large effect, (2) diseases with multifactorial (polygenic) inheritance, and (3) those arising from chromosomal aberrations. The first category, sometimes referred to as *mendelian disorders*, includes many uncommon conditions, such as the storage diseases and inborn errors of metabolism, all resulting from single-gene mutations of large effect. Most of these conditions are hereditary and familial. The second category includes some of the most common disorders of humans, such as hypertension and diabetes mellitus. Multifactorial, or polygenic, inheritance implies that both genetic and environmental influences condition the expression of a phenotypic characteristic or disease. The third category includes disorders that are the consequence of numeric or structural abnormalities in the chromosomes.

To these well-known categories, it is necessary to add a heterogeneous group of genetic disorders that, like mendelian disorders, involve single genes but do not follow simple mendelian rules of inheritance. These single-gene disorders with nonclassic inheritance include those resulting from triplet repeat mutations, those arising from mutations in

include those resulting from triplet repeat mutations, those arising from mutations in mitochondrial DNA, and those in which the transmission is influenced by an epigenetic phenomenon called *genomic imprinting*.

Each of these four categories is discussed separately.



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## MENDELIAN DISORDERS (DISEASES CAUSED BY SINGLE-GENE DEFECT)

Single-gene defects (mutations) follow the well-known mendelian patterns of inheritance. Thus, they are called *mendelian disorders* (Table 7-1). Although individually each is rare, altogether they account for a significant number of admissions to hospitals and about 6% to 8% of all pediatric hospital admissions.

Mutations involving single genes follow one of three patterns of inheritance: autosomal dominant, autosomal recessive, or X-linked. Although gene expression is usually described as dominant or recessive, it should be remembered that a gene pair may be fully expressed in the heterozygote, a condition called *codominance*. Histocompatibility antigens are good examples of codominant inheritance, as well as of *polymorphism* (i.e., the presence of many

A single-gene mutation may lead to many phenotypic effects (*pleiotropy*), and conversely, mutations may affect the same trait (*genetic heterogeneity*).

**Table 7-1. Prevalence of Selected Monogenic Disorders Among Liveborn Infants**

Disorder	Estimated Prevalence
<b>Autosomal Dominant</b>	
Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Huntington disease	1 in 2500
Hereditary spherocytosis	1 in 5000
Marfan syndrome	1 in 20,000
<b>Autosomal Recessive</b>	
Sickle cell anemia	1 in 625 (US blacks)
Cystic fibrosis	1 in 2000 (Caucasians)
Tay-Sachs disease	1 in 3000 (US Jews)
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses (all types)	1 in 25,000
Glycogen storage diseases (all types)	1 in 50,000
Galactosemia	1 in 57,000
<b>X-Linked</b>	
Duchenne muscular dystrophy	1 in 7000
Hemophilia	1 in 10,000

**Table 7-2. Common Autosomal Dominant Disorders**

System	Disorder
Nervous	Huntington disease
	Neurofibromatosis
	Myotonic dystrophy
	Tuberous sclerosis
Urinary	Polycystic kidney disease
Gastrointestinal	Familial polyposis coli
Hematopoietic	Hereditary spherocytosis
	Von Willebrand disease
Skeletal	Marfan syndrome*
	Ehlers-Danlos syndrome (some variants)*



	Osteogenesis imperfecta
	Achondroplasia
Metabolic	Familial hypercholesterolemia*
	Acute intermittent porphyria

\*Discussed in this chapter. Other disorders listed are discussed in appropriate chapters of this book.

For example, Marfan syndrome, which results from a basic defect in connective tissue, is associated with the skeleton, eye, and cardiovascular system, all of which stem from a mutation in the gene encoding the protein fibrillin-1. On the other hand, retinitis pigmentosa, an inherited cause of abnormal retinal pigmentation, can be caused by several different types of mutations. Recognition of genetic heterogeneity not only facilitates the understanding of the pathogenesis of common disorders such as diabetes mellitus

## Transmission Patterns of Single-Gene Disorders

### ***Autosomal Dominant Disorders***

Autosomal dominant disorders are manifested in the heterozygous state, so at least one parent of affected males and females are affected, and both can transmit the condition. When an affected person mates with an unaffected person, there is one chance in two of having the disease. The following features also pertain to autosomal dominant disorders:

With any autosomal dominant disorder, some patients do not have affected parents. Such mutations involving either the egg or the sperm from which they were derived. Their sibling risk of developing the disease is 50%. Clinical features can be modified by reduced penetrance and variable expressivity. Those who inherit the mutant gene but are phenotypically normal. This is referred to as reduced penetrance. Penetrance is not clearly understood. In contrast to penetrance, if a trait is seen in all individuals who express it differently among individuals, the phenomenon is called variable expressivity. For example, in neurofibromatosis 1, the range from brownish spots on the skin to multiple tumors and skeletal deformities. Onset is delayed and symptoms and signs do not appear until adulthood (as in Huntington's disease). In some disorders, a 50% reduction in the normal gene product is associated with clinical symptoms. For example, in some cases, the mutant allele can usually be compensated for, involved genes usually do not encode enzyme proteins. The following features are usually affected in autosomal dominant disorders:

Those involved in regulation of complex metabolic pathways, often subject to feedback inhibition (e.g., receptors and transport proteins). One example of this is familial hypercholesterolemia, a mutation in the low-density lipoprotein (LDL) receptor gene (discussed later). Key structural proteins, such as spectrin, are components of the red cell membrane (e.g., spectrin).

The biochemical mechanisms by which a 50% reduction in the levels of such proteins results in a clinical disorder are not understood. In some cases, especially when the gene encodes one subunit of a multimeric protein, the mutant subunits interfere with the assembly of a functionally normal multimer. For example, the collagen molecule is composed of three chains arranged in a helical configuration. Even with a single mutant collagen chain, normal collagen cannot be formed, hence there is a marked deficiency of collagen. In this instance the mutant allele is called *dominant negative*, because it interferes with the function of a normal allele. This effect is illustrated by some forms of osteogenesis imperfecta (Chap. 10).

### ***Autosomal Recessive Disorders***

Autosomal recessive diseases make up the largest group of mendelian disorders. They occur when both alleles at a locus are mutants; therefore, such disorders are characterized by the following features: (1) The trait is usually not present in the parents but siblings may show the disease; (2) siblings have one chance in four of being affected (i.e., the probability is 1/4); and (3) if the mutant gene occurs with a low frequency in the population, there is a strong likelihood of consanguineous marriage.

In contrast to the features of autosomal dominant diseases, the following features generally apply to autosomal recessive diseases (Table 7-3):

The expression of the defect tends to be more uniform than in autosomal dominant disorders. Onset is frequently early in life. Although new mutations for recessive disorders do occur, they are rare.

Because the affected individual is an asymptomatic heterozygote, several generations may person mate with other heterozygotes and produce affected offspring. In many cases, enzyme In heterozygotes, equal amounts of normal and defective enzyme are synthesized. Usually that cells with half of their complement of the enzyme function normally.

**Table 7-3. Autosomal Recessive Disorders**

System	Disorder
Metabolic*	Cystic fibrosis*
	Phenylketonuria*
	Galactosemia*
	Homocystinuria
	Lysosomal storage diseases*
	$\alpha_1$ -Antitrypsin deficiency
	Wilson disease
	Hemochromatosis
	Glycogen storage diseases*
	Sickle cell anemia
Hematopoietic	Thalassemias
	Congenital adrenal hyperplasia
Endocrine	Ehlers-Danlos syndrome (some variants)*
Skeletal	Alkaptonuria
	Neurogenic muscular
Nervous atrophies	Friedreich ataxia
	Spinal muscular atrophy

\*Discussed in this chapter. Many others are discussed elsewhere in the book.

### ***X-Linked Disorders***

All sex-linked disorders are X-linked. No Y-linked diseases are as yet known. Save for determinator only characteristic that may be located on the Y chromosome is the attribute of hairy ears, which is linked disorders are X-linked recessive and are characterized by the following features (Table 7-4

They are transmitted by heterozygous female carriers only to sons, who of course are hemizygous for the X chromosome. Heterozygous females rarely express the full phenotypic change, because the normal allele is inactivated in most cells, permitting full expression of the disease in heterozygotes. Heterozygous females do not transmit the disorder to sons, but all daughters are carriers. Sons of heterozygous females receive the mutant gene.

**Table 7-4. X-Linked Recessive Disorders**

System	Disease
Musculoskeletal	Duchenne muscular dystrophy
Blood	Hemophilias A and B
	Chronic granulomatous disease
	Glucose-6-phosphate dehydrogenase deficiency
Immune	Agammaglobulinemia
	X-linked severe combined immunodeficiency (SCID)

	Wiskott-Aldrich syndrome
Metabolic	Diabetes insipidus
	Lesch-Nyhan syndrome
Nervous	Fragile X syndrome*

\*Discussed in this chapter.

There are a very few X-linked dominant diseases and they are much less common than disorders inheritance pattern is characterized by transmission of the disease to 50% of the sons and daughter. An affected male cannot transmit the disease to his sons, but all daughters are affected.

Although mendelian disorders are often grouped according to their patterns of transmission, it is possible to group them on the basis of the nature of the protein that is affected, because in large part the type of protein involved determines the inheritance. Hence, in Table 7-5, selected single-gene disorders are classified into broad groupings.

## SUMMARY

**Transmission Patterns of Single-Gene Disorders** Autosomal dominant disorders are expressed in heterozygous state; they affect males and females equally and are transmitted by affected males to 50% of their offspring. Enzyme proteins are not affected in autosomal dominant disorders; receptors and structural proteins are involved. Autosomal recessive disorders require two copies of a gene to be mutated and frequently involve enzyme proteins. Male and female are affected equally. X-linked disorders are transmitted by heterozygous females to their offspring. Female carriers are usually protected because of random inactivation of one X chromosome.

## Diseases Caused by Mutations in Structural Proteins

### Marfan Syndrome

In this autosomal dominant disorder of connective tissues, the basic biochemical abnormality affecting fibroblasts, is the major component of microfibrils found in the extracellular matrix. Microfibrils consist of elastin and are considered integral components of elastic fibers. Fibrillin 1 is encoded by the *FBN1* gene on chromosome 15q21. Mutations in the *FBN1* gene are found in all patients with Marfan syndrome. However, molecular analysis is not feasible, because more than 500 distinct mutations affecting the *FBN1* gene have been found. In the absence of a clear molecular diagnosis, it follows that the mutant fibrillin 1 protein must act as a dominant negative by preventing the synthesis of normal microfibrils.

While many of the abnormalities in Marfan syndrome can be explained on the basis of structural defects, such as overgrowth of bones and myxomatous changes in mitral valves, are difficult to relate to simple models of Marfan syndrome suggest an additional dysregulation of transforming growth factor  $\beta$  ( $TGF-\beta$ ). In the absence of fibrillin-1 there is increased  $TGF-\beta$  production. This cytokine secondarily regulates  $\alpha$ 1(I) procollagen synthesis. In support of this hypothesis, mutations in the  $TGF-\beta$  type II receptor give rise to a related syndrome. The prevalence of Marfan syndrome is estimated to be 1 per 20,000. Approximately 75% of cases are due to new mutations in the germ cells of parents.

Although connective tissue throughout the body is affected, the principal clinical manifestations are in the skeleton, eyes, and the cardiovascular system.

### Morphology

**Skeletal abnormalities** are the most obvious feature of Marfan syndrome. Patients have an elongated habitus with abnormally long legs, arms, and fingers (arachnodactyly); a hyperextensibility of joints. A variety of spinal deformities, such as severe kyphoscoliosis, are common. The chest is deformed, exhibiting either pectus excavatum (i.e., deeply depressed sternum) or pectus carinatum (i.e., protruding sternum). President Lincoln is thought to have had features suggestive of Marfan syndrome. A characteristic **ocular change** is bilateral dislocation, or subluxation, of the lens owing to defects in the suspensory ligaments. It should be noted that the ciliary zonules that support the lens are made up exclusively of fibrillin. Most serious, however, is the involvement of the cardiovascular system. Fragmentation of the elastic fibers in the tunica media of the aorta predisposes to aortic aneurysm and dissection.

**system.** Fragmentation of the elastic fibers in the tunica media of the aorta predisposes to dilation and aortic dissection (Chapter 10). These changes are not specific for Marfan syndrome; lesions occur in patients with hypertension and in aging. Loss of medial support causes dilation of the aortic valve ring, giving rise to aortic incompetence. The cardiac valves, especially the mitral and the tricuspid valve, may be excessively distensible and regurgitant (floppy valve syndrome). Congestive cardiac failure (Chapter 11). Death from aortic rupture may occur at any age; it is a common cause of death. Less commonly, cardiac failure is the terminal event.

Although the lesions described are typical of Marfan syndrome, they are not seen in all patients. There is a wide variation in clinical expression, and some patients may exhibit predominantly cardiac or skeletal or ocular changes. The variable expressivity is believed to be due to mutations in the fibrillin gene.

**Table 7-5. Biochemical Basis and Inheritance Pattern of Some Mendelian Disorders**

Protein Type/Function	Examples	Pattern of Inheritance	Disease
Enzymes	Phenylalanine hydroxylase	Autosomal recessive	Phenylketonuria
	Hexosaminidase		Tay-Sachs disease
	Adenosine deaminase		Severe combined immunodeficiency
Enzyme inhibitor	$\alpha_1$ -Antitrypsin	Autosomal recessive	Emphysema
Receptor	Low-density lipoprotein receptor	Autosomal dominant	Familial hypercholesterolemia
Oxygen transport	Hemoglobin	Autosomal codominant*	$\alpha$ -Thalassemia
			$\beta$ -Thalassemia
			Sickle cell anemia
			Sickle cell trait
Ion transport	Cystic fibrosis transmembrane conductance regulator	Autosomal recessive	Cystic fibrosis
Structural support	Collagen	Autosomal dominant	Osteogenesis imperfecta
			Marfan syndrome
	Fibrillin	Autosomal dominant	Marfan syndrome
Cell membrane	Dystrophin	X-linked recessive	Duchenne's muscular dystrophy
	Spectrin, ankyrin, or protein 4.1	Autosomal dominant	Hereditary spherocytosis
Hemostasis	Factor VIII	X-linked recessive	Hemophilia A
Growth regulation	RB protein	Autosomal dominant	Hereditary retinoblastoma
	NF-1 protein	Autosomal dominant	Neurofibromatosis

\*Heterozygotes either are asymptomatic or have mild disease.

†Some variants of Ehlers-Danlos syndrome are autosomal recessive or X-linked recessive.

### Ehlers-Danlos Syndromes

Ehlers-Danlos syndromes (EDSs) are characterized by defects in collagen synthesis or structure. The mode of inheritance encompasses all three of the mendelian patterns. It should be recalled that all collagen, and all of them have characteristic tissue distributions and are the products of different genes. The heterogeneity of EDS can be explained by mutations in different collagen genes.

At least six clinical and genetic variants of EDS are recognized. Because defective collagen is present in all variants, certain features are common to all.

As might be expected, tissues rich in collagen, such as skin, ligaments, and joints, are frequently involved. Because the abnormal collagen fibers lack adequate tensile strength, *skin is hyperextensible and* permit grotesque contortions, such as bending the thumb backward to touch the forearm and bending the elbow to a right angle. Indeed, it is believed that most contortionists have one of the EDSs; however, a predisposition is paid for this virtuosity. *The skin is extraordinarily stretchable, extremely fragile, and vulnerable*

process part of the vitreous. The skin is extraordinarily stretchable, extremely fragile, and vulnerable to gaping defects, and surgical repair or any surgical intervention is accomplished only with great difficulty and tensile strength. The basic defect in connective tissue may lead to serious internal complications, including aortic aneurysms (vascular EDS); ocular fragility, with rupture of the cornea and retinal detachment (kyphoscoliosis type EDS); and, among others.

The molecular bases of EDS are varied and include the following:

*Deficiency of the enzyme lysyl hydroxylase.* Decreased hydroxylation of lysyl residues in type I collagen leads to decreased normal cross-links among collagen molecules. As might be expected, this variant (kyphoscoliosis type EDS), is inherited as an autosomal recessive disorder. *Deficient synthesis of type III collagen.* This variant (vascular type) is inherited as an autosomal dominant disorder. It affects tissues rich in type III collagen (e.g., blood vessels, bowel wall). *Defective conversion of procollagen to collagen.* A mutation in two type I collagen genes (*COL1A1* and *COL1A2*) in arthrochalasia-type EDS.

## SUMMARY

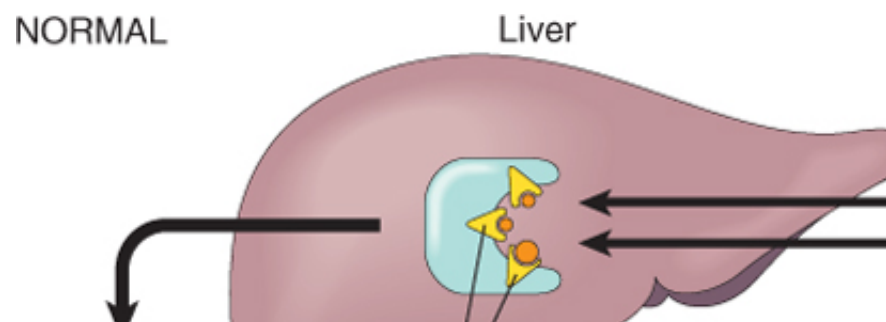
**Marfan Syndrome** Marfan syndrome is caused by a mutation in the gene encoding for the protein required for structural integrity of connective tissues. The major tissues affected are the heart and cardiovascular system. Clinical features include tall stature, long fingers, lens dislocation, floppy mitral valve, aortic aneurysm, and aortic dissection.

**Ehlers-Danlos Syndromes** There are six variants of Ehlers-Danlos syndrome. Each of the variants is caused by a disturbance in collagen synthesis or assembly. Common clinical features are fragile, hyperextensible skin vulnerable to trauma, hypermobile joints, and internal organs like colon, cornea, and large arteries. Wound healing is poor.

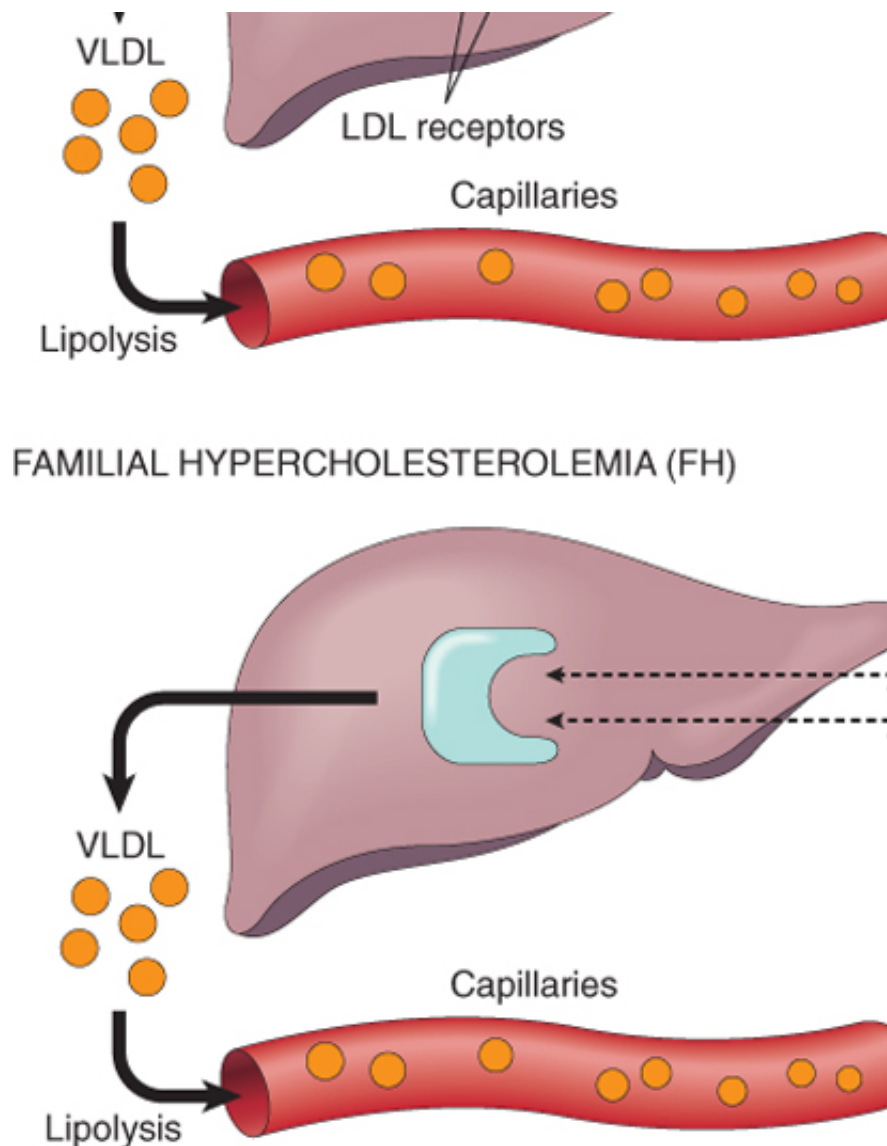
## Diseases Caused by Mutations in Receptor Proteins

### Familial Hypercholesterolemia

Familial hypercholesterolemia is among the most common mendelian disorders; the frequency of the disorder is 1 in 250 in the general population. It is caused by a mutation in the gene that specifies the receptor for LDL, the low-density lipoprotein, which transports cholesterol. As you know, cholesterol may be derived from the diet or from endogenous synthesis. Cholesterol is incorporated into chylomicrons in the intestinal mucosa, which drain via the lymphatic system. Chylomicrons are hydrolyzed by an endothelial lipoprotein lipase in the capillaries of muscle and fat tissue. The products, free cholesterol and fatty acids, are then delivered to the liver. Some of the cholesterol enters the metabolic pool (to be used for steroid synthesis or converted to bile acids into the biliary tract). The endogenous synthesis of cholesterol and LDL is the secretion of triglyceride-rich very-low-density lipoprotein (VLDL) by the liver. In the capillaries of adipose tissue and muscle, the VLDL particle undergoes lipolysis and is converted to intermediate-density lipoprotein (IDL). Compared with VLDL, the content of triglyceride is reduced and that of cholesterol esters is enriched. Further metabolism of IDL occurs also in the capillaries. Some IDL particles are taken up by the liver through the LDL receptor described later; others are converted to high-density lipoprotein (HDL) by the action of lipoprotein lipase and apolipoprotein E. In the liver cells, IDL is recycled to generate VLDL.



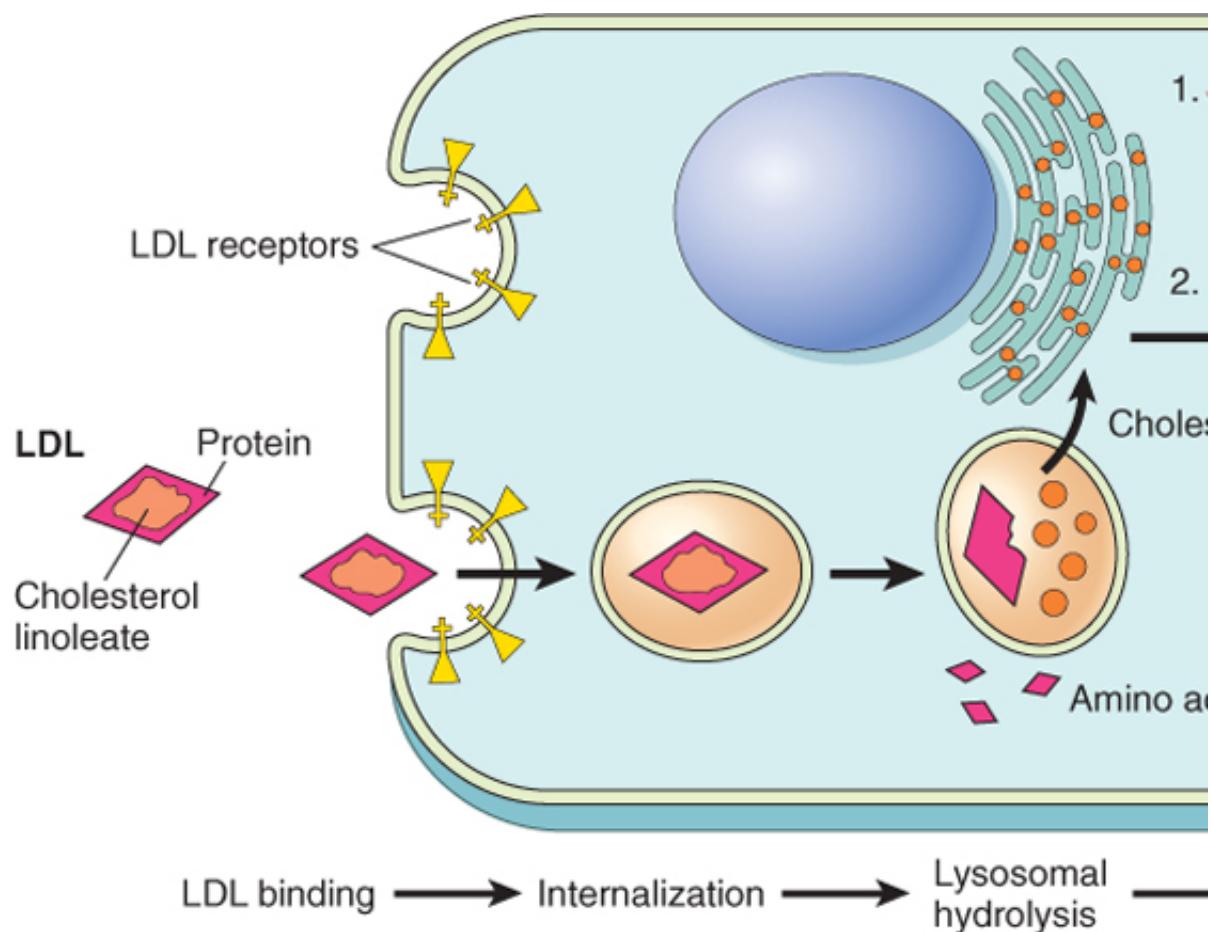




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 Figure 7-2 Low-density lipoprotein (LDL) metabolism and the role of the liver in its synthesis and catabolism: familial hypercholesterolemia. IDL, intermediate-density lipoprotein; VLDL, very-low-density lipoprotein.

Two-thirds of the resultant LDL particles are metabolized by the LDL receptor pathway, and the remainder is taken up by the scavenger receptors, to be described later. The LDL receptor binds to apolipoprotein B-100 on the surface of the LDL particle, mediating the transport of both LDL and IDL. Although the LDL receptors are widely distributed, approximately 70% of the receptors are located on the surface of the liver. The liver plays an extremely important role in LDL metabolism. The first step in the receptor-mediated pathway is the binding of the LDL particle to the cell surface receptor, followed by endocytotic internalization (Fig. 7-3). Within the cell, the endocytotic vesicle fuses with a lysosome, and the LDL molecule is enzymatically degraded, resulting ultimately in the release of free cholesterol. The cholesterol is not only used by the cell for membrane synthesis but also takes part in intracellular cholesterol feedback control:

It suppresses cholesterol synthesis by inhibiting the activity of the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), which is the rate-limiting enzyme in the synthetic pathway for cholesterol. It also inhibits the activity of cholesterol acyltransferase (ACAT), which favors esterification and storage of excess cholesterol. The liver also increases the number of cell surface LDL receptors, thus protecting cells from excessive accumulation of cholesterol.



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Figure 7-3 Sequential steps in low-density lipoprotein (LDL) pathway in mammalian cells. The arrows show the sequential steps: (1) LDL binding to receptors, (2) internalization of LDL by receptors, (3) suppression of cholesterol synthesis by inhibition of HMGCoA reductase, (4) storage of excess cholesterol by active receptors. ACAT, acyl-CoA:cholesterol acyltransferase; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase. Brown MS: The LDL receptor defect in familial hypercholesterolemia. Implications for pathogenesis and the

The transport of LDL by the scavenger receptors, alluded to earlier, seems to take place in cells or possibly in other cells as well. Monocytes and macrophages have receptors for chemically modified LDL. The amount catabolized by this "scavenger receptor" pathway is directly related to the plasma cholesterol level.

In familial hypercholesterolemia, mutations in the LDL receptor gene impair the intracellular transport and catabolism of LDL, leading to accumulation of LDL cholesterol in the plasma. In addition, the absence of LDL receptors on liver cells leads to a greater proportion of plasma IDL being converted into LDL. Thus, patients with familial hypercholesterolemia have excessive levels of serum cholesterol as a result of the combined effects of reduced catabolism and increased production. In the presence of such hypercholesterolemia, there is a marked increase of cholesterol traffic into the arterial wall via the scavenger receptor. This accounts for the appearance of skin xanthomas and

Familial hypercholesterolemia is an autosomal dominant disease. Heterozygotes have a two- to threefold elevation of serum cholesterol levels, whereas homozygotes may have in excess of a fivefold elevation. Although heterozygotes remain asymptomatic until adult life, when they develop cholesterol deposits (xanthomas) and premature atherosclerosis resulting in coronary artery disease. Homozygous persons are much more severely affected, developing cutaneous xanthomas in childhood and often dying of myocardial infarction by the age of 15 years.

Analysis of the cloned LDL receptor gene has revealed that more than 900 different mutations can cause familial hypercholesterolemia. These can be grouped in five categories. Class I mutations are uncommon and affect receptor synthesis. With class II mutations, the most prevalent form, the receptor protein is synthesized

endoplasmic reticulum to the Golgi apparatus is impaired. Class III mutations produce receptors that fail to bind LDL normally. Class IV mutations give rise to receptors that fail to internalize after binding. Class V mutations encode receptors that can bind LDL and are internalized but are trapped in endosomes because recycling does not occur.

The discovery of the critical role of LDL receptors in cholesterol homeostasis has led to the rational use of statins, which are now widely used to lower plasma cholesterol. They inhibit the activity of HMG-CoA reductase, the rate-limiting enzyme in LDL receptor synthesis (see Fig. 7-3).

### SUMMARY

**Familial Hypercholesterolemia** Familial hypercholesterolemia is an autosomal recessive disorder caused by mutations in the LDL receptor gene. Patients develop hypercholesterolemia and transport of LDL into the cells. In heterozygotes, elevated serum cholesterol leads to atherosclerosis and resultant coronary artery disease; homozygotes have even higher serum cholesterol and occurrence of ischemic heart disease. Cholesterol crystals in tendon sheaths produce xanthomas.

## Diseases Caused by Mutations in Enzyme Proteins

### Phenylketonuria

There are several variants of this inborn error of metabolism, which affects 1 in 12,000 live-born Caucasians. The most common form, referred to as *classic phenylketonuria* (PKU), is quite common in persons of Scandinavian descent, blacks and Jews.

Homozygotes with this autosomal recessive disorder classically have a severe lack of phenylalanine hydroxylase, hyperphenylalaninemia and PKU. Affected infants are normal at birth but within a few weeks develop symptoms which in some way impairs brain development. Usually by 6 months of life *severe mental retardation* develops. About 4% of untreated phenylketonuric children have IQs greater than 50 or 60. About one-third of these children cannot talk. *Seizures*, other neurologic abnormalities, *decreased pigmentation of hair and skin*, and *mental retardation* in untreated children. Hyperphenylalaninemia and the resultant mental retardation can be prevented by early phenylalanine intake early in life. Hence, several screening procedures are routinely performed to detect PKU in newborns.

Many female PKU patients, treated with diet early in life, reach childbearing age and are clinically normal. However, because dietary treatment is discontinued after they reach adulthood, they become mentally retarded and have multiple congenital anomalies, even though the infants themselves are normal. This condition, *maternal PKU*, results from the teratogenic effects of phenylalanine that crosses the placenta and is an imperative that maternal phenylalanine levels be lowered by dietary means before conception. Maternal PKU increases the risk of spontaneous abortions.

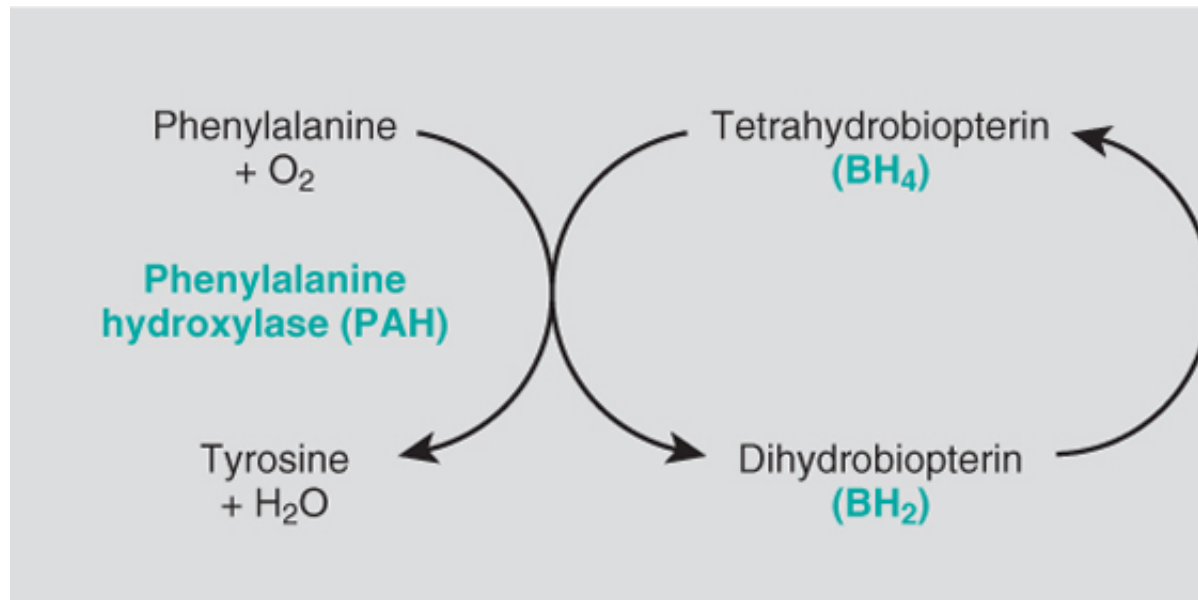
The biochemical abnormality in PKU is an inability to convert phenylalanine into tyrosine. In normal metabolism, phenylalanine intake is necessary for protein synthesis. The remainder is converted to tyrosine (Fig. 7-4). When phenylalanine metabolism is blocked because of a lack of phenylalanine hydroxylase, yielding several intermediates that are excreted in large amounts in the urine and in the sweat, giving a *musty odor* to affected infants. It is believed that excess phenylalanine or its metabolites contribute to the mental retardation. Tyrosine (see Fig. 7-4), a precursor of melanin, is responsible for the light color of hair and skin.

At the molecular level, approximately 400 mutant alleles of the phenylalanine hydroxylase gene have been identified. Some cause a severe deficiency of the enzyme and thus result in classic PKU. In those with a partial deficiency, only modest elevations of phenylalanine levels occur, and there is no neurologic damage. This condition, *hyperphenylalaninemia*, is important to recognize because affected individuals may test positive in the Guthrie test, a stigmata of classic PKU. Measurement of serum phenylalanine levels is necessary to differentiate between classic PKU and *hyperphenylalaninemia*. Because of the numerous disease-causing alleles of the phenylalanine hydroxylase gene, once a biochemical diagnosis is established, the specific mutation causing PKU can be determined. With

family members can be performed.

As alluded to earlier, several variant forms of PKU have been identified. These account for 2% to deficiencies of enzymes other than phenylalanine hydroxylase, such as dihydropteridine reductase. *recognize these variant forms of PKU, because they cannot be treated by dietary restriction of phenylalanine.*

### Galactosemia



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Figure 7-4 The phenylalanine hydroxylase system. NAD(H), Nicotinamide adenine dinuc

Galactosemia is an autosomal recessive disorder of galactose metabolism that affects one in 30,000. It splits lactose, the major carbohydrate of mammalian milk, into glucose and galactose in the intestine. Galactose is then converted to glucose in several steps, in one of which the enzyme galactose-1-phosphate uridylyl transferase is responsible for galactosemia. As a result of this lack of transferase, galactose 1-phosphate and galactitol, accumulate in many tissues, including the liver, spleen, lens of the eye, kidney, and cerebellum.

The liver, eyes, and brain bear the brunt of the damage. The early-developing hepatomegaly is due to widespread scarring that closely resembles the cirrhosis of alcohol abuse may supervene (Chapter 10). Cataracts develop, probably because the lens absorbs water and swells as galactitol, produced and accumulates and increases its tonicity. Nonspecific alterations appear in the central nervous system, including gliosis, and edema. There is still no clear understanding of the mechanism of injury to the liver and brain.

Almost from birth, these infants fail to thrive. Vomiting and diarrhea appear within a few days of life. Usually become evident during the first week of life. Accumulation of galactose and galactose 1-phosphate in the blood, resulting in aminoaciduria. There is an increased frequency of fulminant *Escherichia coli* infection. With therapy, long-term complications such as cataracts, speech defects, neurologic deficits, and ovarian dysfunction.

Most of the clinical and morphologic changes can be prevented by early removal of galactose from the diet. The diagnosis is established by assay of the transferase in leukocytes and erythrocytes. Ante-natal diagnosis by amniocentesis or DNA-based testing of cultured amniocytes or chorionic villi.

### SUMMARY

**Phenylketonuria** Phenylketonuria is an autosomal recessive disorder caused by a deficiency of phenylalanine hydroxylase and consequent inability to metabolize phenylalanine.

include severe mental retardation, seizures, and decreased pigmentation of the skin. Treatment is achieved by restricting the intake of phenylalanine in the diet. Female PKU patients without treatment can give birth to mentally retarded children with malformations due to the passage of phenylalanine metabolites.

**Galactosemia** Galactosemia is caused by an inherited lack of galactose-1-phosphate uridylyltransferase causing accumulation of galactose 1-phosphate and its metabolites in various tissues. Clinical features include jaundice, liver damage, cataracts, neural damage, diarrhea, and *E. coli* sepsis. Dietary restriction of galactose can prevent the disease.

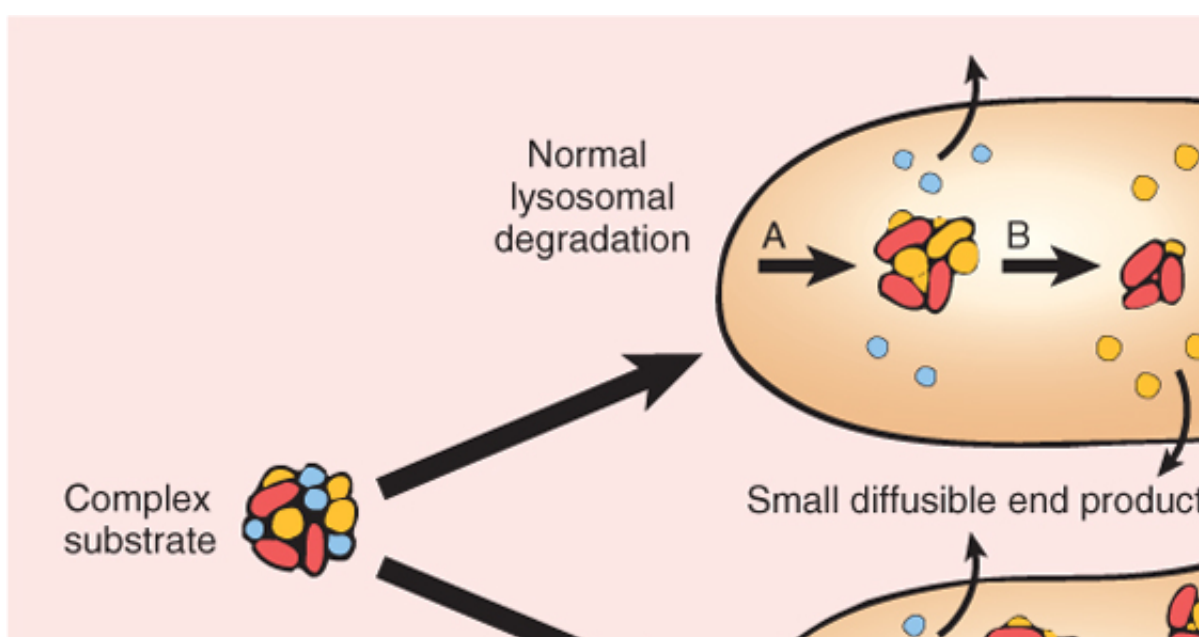
### Lysosomal Storage Diseases

Lysosomes, as is well known, contain a variety of hydrolytic enzymes that are involved in the breakdown of sphingolipids and mucopolysaccharides, into soluble end products. These large molecules may be taken up by organelles that enter the lysosomes by autophagocytosis, or they may be acquired from outside the cell. In the case of an inherited lack of a lysosomal enzyme, catabolism of its substrate remains incomplete, leading to the accumulation of insoluble metabolites within the lysosomes (Fig. 7-5). Approximately 40 lysosomal storage diseases are known, each resulting from the functional absence of a specific lysosomal enzyme or proteins involved in their function. They are divided into broad categories based on the biochemical nature of the substrates and the accumulation mechanism. The mechanistic classification is based on the underlying molecular defect (Table 7-6). Within each group, there are many specific diseases, each resulting from the deficiency of a specific enzyme. Despite this complexity, certain features are common to all lysosomal storage diseases.

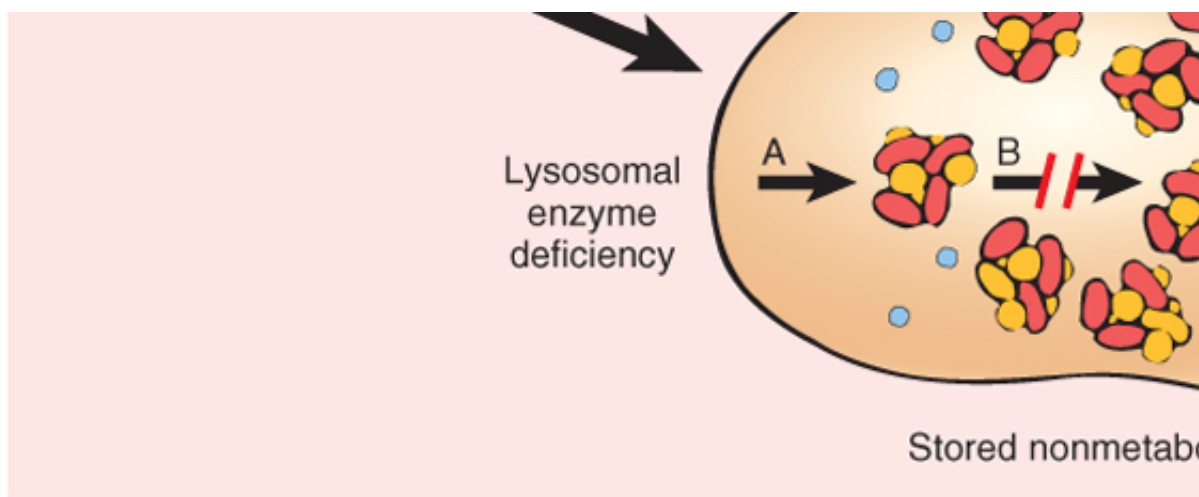
Autosomal recessive transmission Commonly affect infants and young children Storage of undigested material in the mononuclear phagocyte system, giving rise to hepatosplenomegaly Frequent CNS involvement due to storage of material in the brain Cellular dysfunctions, caused not only by storage of undigested material but also by the release of cytokines triggered, for example, by macrophage activation and release of cytokines.

Fortunately for both medical students and the potential victims of the diseases, most of these conditions have been described in detail in the literature. A description is better relegated to specialized texts and reviews. Only a few of the more common conditions are discussed here. The glycogen storage disease (Pompe disease), also a lysosomal disorder, is discussed later.

*Tay-Sachs Disease (GM2 Gangliosidosis: Deficiency in Hexosaminidase A Subunit)*







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 Figure 7-5 Pathogenesis of lysosomal storage diseases. In this example, a complex substrate is normally degraded into soluble end products. If there is a deficiency or malfunction of one of the enzymes (e.g., B), catabolism is incomplete and the substrate is stored in the lysosomes.

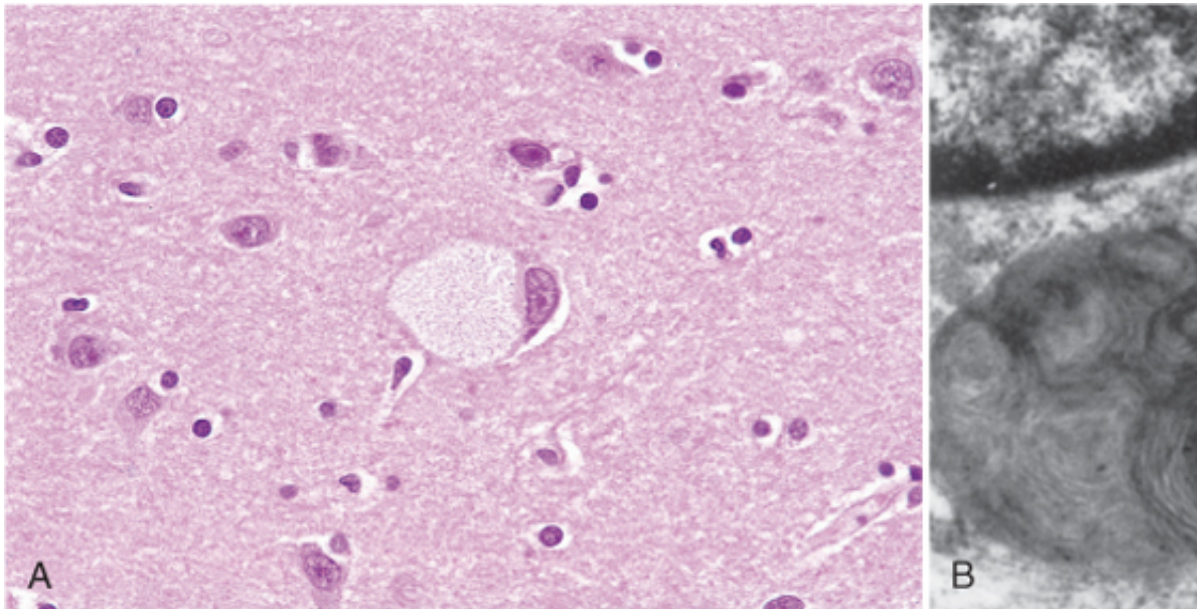
Gangliosidoses are characterized by accumulation of gangliosides, principally in the brain, as a result of a deficiency of a lysosomal enzyme. Depending on the ganglioside involved, these disorders are subclassified into different types. The most common of all gangliosidoses, is characterized by a mutation in and consequent deficiency of the enzyme hexosaminidase A, which is necessary for the degradation of  $G_{M2}$ . More than 90 mutations have been identified, affecting protein folding or intracellular transport. The brain is principally affected, because it is most involved in the *storage of  $G_{M2}$*  occurs within neurons, axon cylinders of nerves, and glial cells throughout the CNS, giving the brain a foamy (Fig. 7-6A). Electron microscopy reveals a whorled configuration within lysosomes (Fig. 7-6B) throughout the CNS (including the spinal cord), peripheral nerves, and autonomic nervous system.

**Table 7-6. Lysosomal Storage Disorders**

Disease category	Disease	Deficiency
Primary lysosomal hydrolase defect	Gaucher disease	Glucosylceramidase
	GM1 gangliosidosis	$G_{M1}$ - $\beta$ -galactosidase
	Tay-Sachs disease	$\beta$ -Hexosaminidase A
	Sandhoff disease	$\beta$ -Hexosaminidase B
	Fabry disease	$\alpha$ -Galactosidase
	Krabbe disease	$\beta$ -Galactosyl ceramidase
	Niemann-Pick disease types A and B	Sphingomyelinase
Post-translational processing defect of lysosomal enzymes	Mucopolysaccharidosis	Multiple sulfatase
Trafficking defect for lysosomal enzymes	Mucopolysaccharidosis types II and IIIA	<i>N</i> -acetyl glucosaminidase
Defect in lysosomal enzyme protection	Galactosialidosis	Protective protein (neuraminidase)
Defect in soluble nonenzymatic lysosomal proteins	GM2 activator protein deficiency, variant AB	GM2 activator protein
	Sphingolipid activator protein deficiency	Sphingolipid activator protein
Transmembrane (nonenzymic) protein	Niemann-Pick disease type C (NPC)	<i>NPC1</i> and <i>NPC2</i>
	Sialidosis (free sialic acid storage)	Sialin

Modified from Jeyakumar M, et al: Storage solutions: treating lysosomal disorders of the brain. *Nature Rev Neurosci* 6:1, 2005.

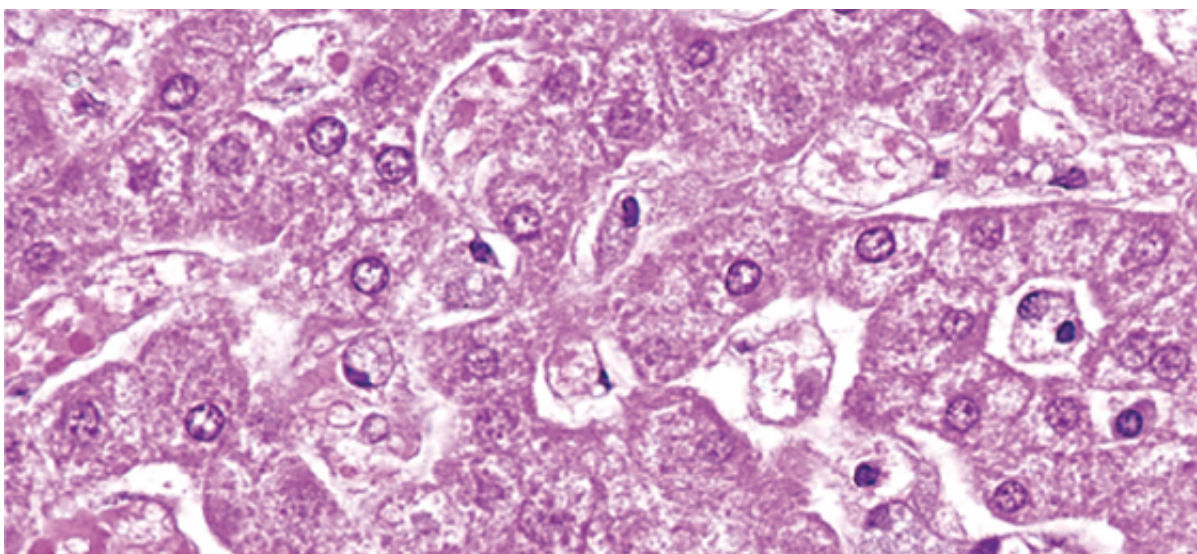
The molecular bases of neuronal injury are not fully understood. Because in many cases the mutation is called "unfolded protein" response ([Chapter 1](#)). If such misfolded proteins are not stabilized by chaperones, these findings have given rise to the possibility of chaperone therapy for this and similar lysosomal storage disorders.



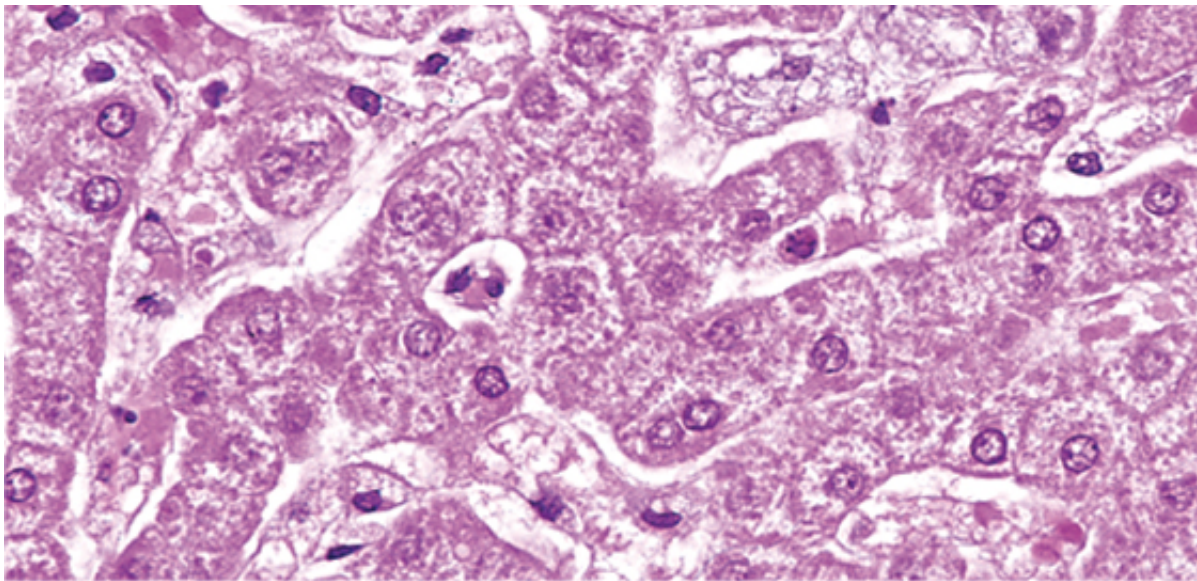
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Figure 7-6 **A**, Ganglion cells in Tay-Sachs disease. Under the light microscope, a large neuron has obvious lipid vacuolation. **B**, A neuron under the electron microscope shows prominent lysosomes with whorled configurations. Part of the nucleus is visible. (Reprinted from Weinberg, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas. **B** Courtesy of Dr. J. H. Garfield, University of Washington Medical Center, Seattle, Washington.)

Tay-Sachs disease, like other lipidoses, is most common among Ashkenazi Jews, among whom it is estimated to be one in 30. Heterozygotes can be reliably detected by estimating the level of hexosaminidase A activity. In the most common acute infantile variant of Tay-Sachs disease, infants appear normal until 6 months of age, followed by mental retardation, blindness, and severe neurologic dysfunctions.

#### *Niemann-Pick Disease, Types A and B*







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 Figure 7-7 Niemann-Pick disease in liver. The hepatocytes and Kupffer cells have a foamy, vacuolated appearance.  
 Dr. Arthur Weinberg, Department of Pathology, University of Texas Southwestern Medical

These two related entities are characterized by a primary deficiency of acid sphingomyelinase and sphingomyelin. In type A, characterized by a severe deficiency of sphingomyelinase, the breakdown of sphingomyelin to sphingosine and phosphorylcholine is impaired, and excess sphingomyelin accumulates in all phagocytic cells and become stuffed with droplets or particles of the complex lipid, imparting a fine vacuolation or foam cell appearance. Because of their high content of phagocytic cells, *the organs most severely affected are the spleen and lungs*. The splenic enlargement may be striking. In addition, the entire CNS, including the spinal cord, is involved in an inexorable process. The affected neurons are enlarged and vacuolated as a result of the storage of sphingomyelin. In infancy with *massive visceromegaly and severe neurologic deterioration*. Death usually occurs within a few years of birth. In comparison, patients with the type B variant have organomegaly but no neurologic symptoms. Esophageal biopsies, leukocytes or cultured fibroblasts can be used for diagnosis of suspected cases, as well as for confirmation by enzyme assays or DNA probe analysis.

#### *Niemann-Pick Disease Type C*

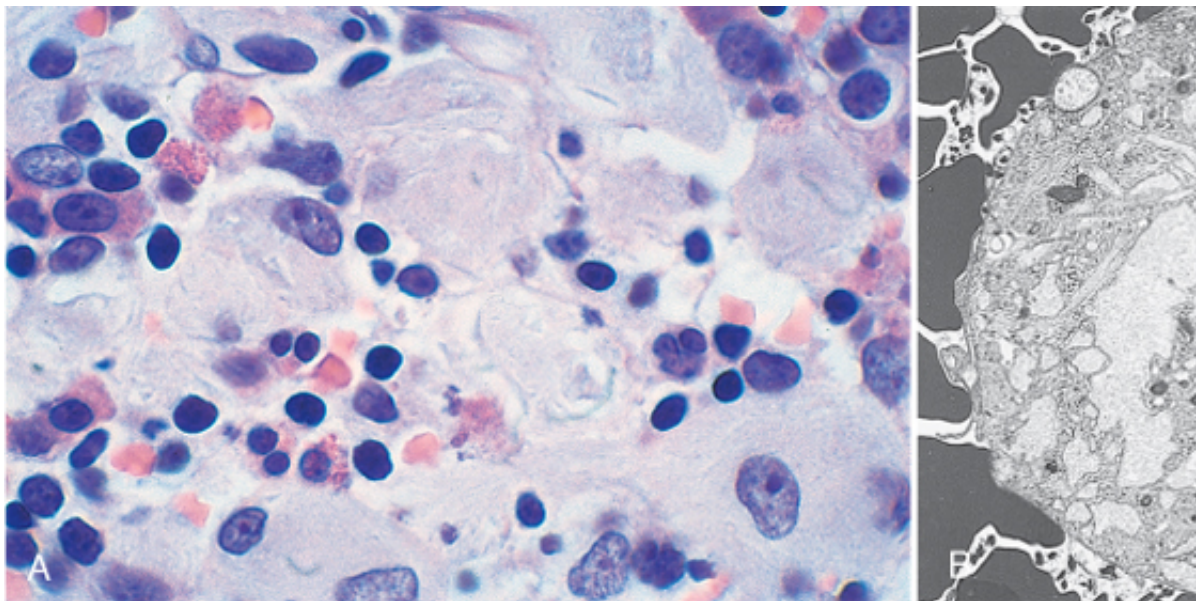
Although previously considered to be related to types A and B Niemann-Pick disease, type C (NPC) is a distinct entity with its own molecular levels and is more common than types A and B combined. Mutations in two related genes, *NPC1* and *NPC2*, are responsible for the majority of cases. Unlike most other lysosomal storage diseases, NPC involves a defect in lipid transport. Affected cells accumulate cholesterol as well as gangliosides such as  $GM_1$  and  $GM_2$ . The exact mechanism by which the *NPC1* gene is still not clear. NPC is clinically heterogeneous: the most common form presents with vertical supranuclear gaze palsy, dystonia, dysarthria, and psychomotor regression.

#### *Gaucher Disease*

This disease results from mutation in the gene that encodes glucosylceramidase. There are five distinct forms of the disease resulting from distinct allelic mutations. Common to all is a variably deficient activity of a glucosylceramidase enzyme that removes a glucose residue from ceramide. This leads to an accumulation of glucosylceramide in the macrophages, which are transformed into so-called Gaucher cells. Normally the glycolipids derived from the breakdown of red blood cells (erythrocytes), are sequentially degraded. In Gaucher disease, the degradation stops at the level of glucosylceramide. These phagocytes (Gaucher cells) become enlarged, with some becoming as large as 100  $\mu m$ , but they are still within the lysosomes, and develop a pathognomonic cytoplasmic appearance characterized as "wrinkled tissue paper" inclusions. It is evident now that Gaucher disease is caused not just by the burden of the disease on the macrophages. High levels of macrophage-derived cytokines, such as interleukins (IL-2, IL-6) and

in affected tissues.

One variant, type I, also called the *chronic non-neuronopathic form*, accounts for 99% of cases of clinical or radiographic bone involvement (osteopenia, focal lytic lesions, and osteonecrosis) in 70% are hepatosplenomegaly and the absence of CNS involvement. The spleen often enlarges massively. Foamy cells are found in the liver, spleen, lymph nodes, and bone marrow. Marrow replacement and corticosteroid-responsive skeletal lesions, as well as a reduction in the formed elements of blood. Bone changes are derived from cytokines, listed above. Type I is most common in Ashkenazi Jews and, unlike other variants, type II and III are characterized by neurologic signs and symptoms. In type II, the symptoms start severe, whereas in type III, the symptoms appear later and are milder. Although the liver and spleen are dominated by neurologic disturbances. In addition to these, there is a perinatal-lethal form characterized by skeletal lesions, and non-immune hydrops (see later). In the so-called cardiovascular form, there is involvement of heart valves.



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Figure 7-8 Gaucher disease involving the bone marrow. **A**, Gaucher cells with abundant lipid-laden granular cytoplasm and elongated distended lysosomes. (Courtesy of Dr. Mathew Fries, Department of Pathology, University of Texas at San Antonio)

The level of glucosylceramidase in leukocytes or cultured fibroblasts is helpful in diagnosis and in therapy is aimed at enzyme replacement by infusion of purified enzyme. A newer form of therapy (glucosylceramide) by administration of drugs that inhibit glucosylceramide synthetase. Since glucosylceramide accumulation is also reduced. On the horizon is glucosylceramidase gene therapy involving infusion of cells transfected with the normal gene.

### Mucopolysaccharidoses

Mucopolysaccharidoses (MPSs) are characterized by defective degradation (and therefore excess accumulation) of various tissues. Recall that mucopolysaccharides form a part of ground substance and are synthesized by chondrocytes. Most of the mucopolysaccharide is secreted into the ground substance, but a certain fraction is degraded by enzymes. Several clinical variants of MPS, classified numerically from MPS I to MPS VII, have the deficiency of one specific enzyme. The mucopolysaccharides that accumulate within the tissues are hyaluronic acid, chondroitin sulfate, keratan sulfate, and (in some cases) chondroitin sulfate.

In general, the MPSs are progressive disorders characterized by involvement of many organs, including the heart, lungs, and blood vessels. Most are associated with *coarse facial features, clouding of the cornea, joint stiffness, and* the accumulated mucopolysaccharides is often increased. All of these disorders except one are inherited as autosomal recessive traits.

conditions; the exception, Hunter syndrome, is an X-linked recessive disease. Of the seven recognized characterized syndromes are discussed briefly here.

Mucopolysaccharidosis type I refers to a spectrum of three disorders varying from mild to severe, iduronidase. At the two ends of the spectrum are Hurler syndrome and Scheie syndrome, with the middle position. In Hurler syndrome, affected children have a life expectancy of 6 to 10 years. Like they develop coarse facial features associated with skeletal deformities. Death is often due to cardiovascular formation of raised endothelial and endocardial lesions by the deposition of mucopolysaccharides. Accumulation of dermatan sulfate and heparan sulfate is seen in cells of the mononuclear phagoc endothelium and smooth muscle cells of the vascular wall. The affected cells are swollen and have accumulation of material positive for periodic acid-Schiff stain within engorged, vacuolated lysosomes in neurons, accounting for the mental retardation.

The other variant of MPS, called type II, or *Hunter syndrome*, differs from Hurler syndrome in its absence of corneal clouding, and often its milder clinical course. As in Hurler syndrome, the accumulated syndromes are heparan sulfate and dermatan sulfate, but this results from a deficiency of L-iduronidase; enzyme deficiency, an accumulation of identical substrates occurs because breakdown of heparan sulfate by both  $\alpha$ -L-iduronidase and the sulfatase; if either one is missing, further degradation is blocked.

### SUMMARY

**Lysosomal Storage Diseases** *Tay-Sachs disease* is caused by an inability to degrade gangliosides due to lack of lysosomal hexosaminidase A.  $G_{M2}$  gangliosides accumulate and cause severe mental retardation, blindness, motor weakness, and death in early age. *Niemann-Pick disease types A and B* are caused by a deficiency of sphingomyelinase. In the more severe type A variant, accumulation of sphingomyelin in the nervous system causes damage. Lipid is also stored in phagocytes within the liver, spleen, bone marrow, causing their enlargement. In type B, neuronal damage is not present. *Niemann-Pick disease type C* is caused by a defect in cholesterol transport and resultant accumulation of cholesterol in the nervous system. Affected children have ataxia, dysarthria, and psychomotor regression. *Gaucher disease* results from lack of the lysosomal enzyme glucocerebrosidase. Accumulation of glucosylceramide in mononuclear phagocytic cells. In the severe variant, affected phagocytes become enlarged (Gaucher cells) and accumulate in the bone marrow, causing hepatosplenomegaly and bone erosion. Type II and III involve the nervous system. *Mucopolysaccharidoses* result from accumulation of mucopolysaccharides in various tissues including liver, spleen, heart, blood vessels, brain, cornea, and joints. All forms have coarse facial features. In Hurler syndrome there is corneal clouding, valvular depositions, and death in childhood. Hunter syndrome has a milder course.

### **Glycogen Storage Diseases (Glycogenoses)**

An inherited deficiency of any one of the enzymes involved in glycogen synthesis or degradation or an abnormal form of glycogen in various tissues. The type of glycogen stored, its distribution, and the distribution of the affected cells vary depending on the specific enzyme deficiency. Regardless of the type, glycogen is most often stored within the cytoplasm, or sometimes within nuclei. One variant, Pompe disease, is an exception because the missing enzyme is localized to lysosomes. Most glycogenoses are inherited as autosomal recessive with "missing enzyme" syndromes.

Approximately a dozen forms of glycogenoses have been described on the basis of specific enzyme pathophysiology, they can be grouped into three categories (Table 7-7):

**Hepatic type.** Liver contains several enzymes that synthesize glycogen for storage and also release it. Hence, a deficiency of the hepatic enzymes involved in glycogen metabolism is associated with enlargement of the liver due to storage of glycogen and hypoglycemia due to a failure of release.



enlargement of the liver due to storage of glycogen and hypoglycemia due to a failure of glucose-6-phosphatase, is the most common form of glycogenosis (see Table 7-7). **Myopathic type.** In striated muscle, glycogen is an important energy source. Several forms of glycogen storage disease affect muscles. When enzymes that are involved in glycogen metabolism are deficient, a myopathy occurs in muscles and there is an associated muscle weakness due to impaired energy production. **Common features of glycogen storage diseases are marked by muscle cramps after exercise, myoglobinuria, and elevation in blood lactate levels because of a block in glycolysis.** McArdle disease (type V glycogenosis) is the prototype of myopathic glycogenoses. Two other forms of myopathic glycogenosis are described. Type II glycogenosis (*Pompe disease*) is caused by a deficiency of the enzyme associated with degradation of glycogen in virtually every organ, but cardiomegaly is most prominent. Type III glycogenosis is caused by deposition of an abnormal form of glycogen, with detrimental effects on the liver.

**Table 7-7. Principal Subgroups of Glycogenoses**

Clinicopathologic Category	Specific Type	Enzyme Deficiency	Morphologic Changes	Clinical Features
Hepatic type	Hepatorenal (von Gierke disease, type I)	Glucose-6-phosphatase	Hepatomegaly: intracytoplasmic accumulations of glycogen and small amounts of lipid; intranuclear glycogen Renomegaly: intracytoplasmic accumulations of glycogen in cortical tubular epithelial cells	In untreated: growth retardation, hypoglycemia, mobilization of fat, hyperlipidemia, derangement of development, bleeding tendency. With treatment: growth, glucose tolerance improves
Myopathic type	McArdle syndrome (type V)	Muscle phosphorylase	Skeletal muscle only—accumulations of glycogen predominant in subsarcolemmal location	Painful cramps on exercise, myoglobinuria, onset in childhood, muscular weakness, venous thrombosis, compatible with life
Miscellaneous type	Generalized glycogenosis (Pompe disease, type II)	Lysosomal glucosidase (acid maltase)	Mild hepatomegaly: ballooning of lysosomes with glycogen creating a foamy cytoplasmic pattern Cardiomegaly: glycogen within sarcoplasm as well as membrane-bound Skeletal muscle: similar to heart (see cardiomegaly)	Massive cardiomegaly, mild renal involvement

## SUMMARY

**Glycogen Storage Diseases** Inherited deficiency of enzymes involved in glycogen metabolism result in storage of normal or abnormal forms of glycogen, predominantly in liver and muscle tissues. In the *hepatic form* (von Gierke disease), liver cells store glycogen because of a deficiency of hepatic glucose-6-phosphatase. There are several *myopathic forms*, including McArdle disease, in which muscle phosphorylase deficiency gives rise to storage in skeletal muscles and associated muscle weakness. In *Pompe disease* there is lack of lysosomal acid maltase, and all organs are affected, with liver involvement being predominant.

## Diseases Caused by Mutations in Proteins That Regulate Cell Growth

As was detailed in Chapter 6, two classes of genes, proto-oncogenes and tumor suppressor genes, regulate cell growth and differentiation. Mutations affecting these genes, most often in somatic cells, are involved in the pathogenesis of cancer. About 5% of all cancers, however, mutations affecting certain tumor suppressor genes are present in all cells of the body and hence can be transmitted to the offspring. These mutant genes predispose the offspring to hereditary cancer.

greater detail in [Chapter 6](#).



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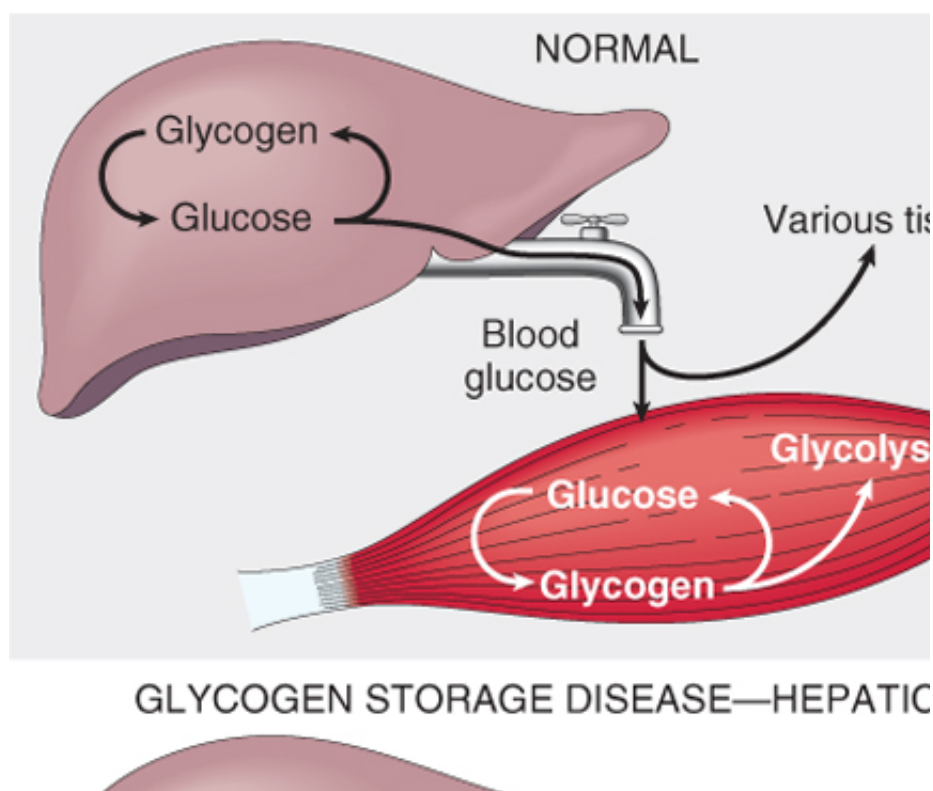


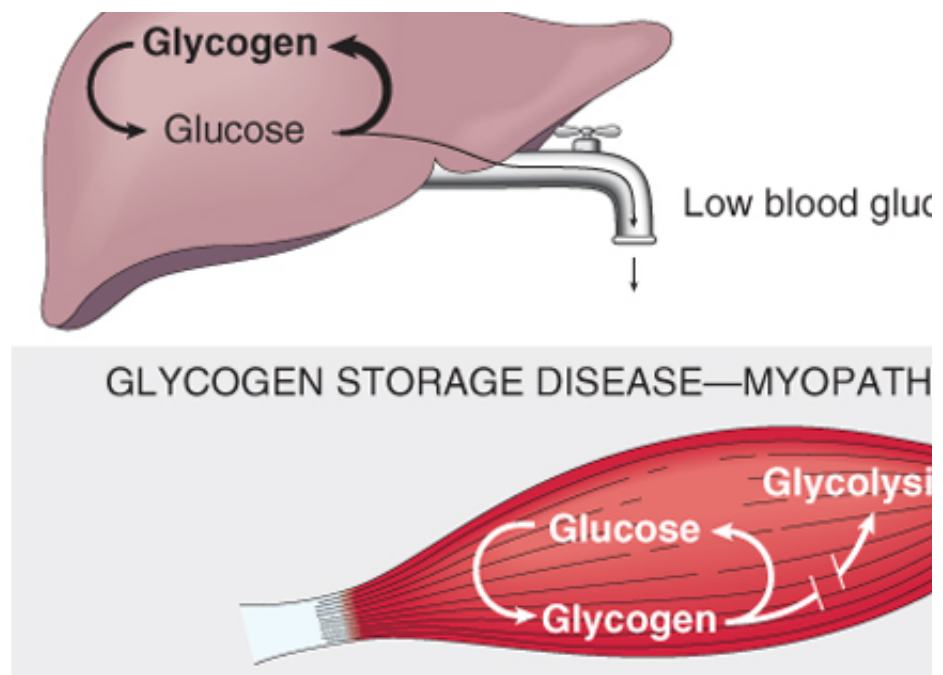
## DISORDERS WITH MULTIFACTORIAL INHERITANCE

Multifactorial (also called *polygenic*) inheritance is involved in many of the physiologic characteristics (e.g., blood pressure, hair color). A multifactorial physiologic or pathologic trait may be defined as one governed by many genes of small effect, conditioned by environmental, nongenetic influences. Even monozygous twins can have different heights because of nutritional or other environmental influences. When surveyed in a large population, traits governed by multifactorial inheritance fall on a continuous Gaussian distribution (Fig. 7-10). Presumably, a disorder becomes manifest only when a certain number of effector genes, as well as conditions, are involved. The threshold effect also explains why parents of a child with a polygenic disorder may not be affected. Once a threshold value is exceeded, the severity of the disease is directly proportional to the number and type of genes.

The following features characterize multifactorial inheritance. These have been established for the malformations and, in all likelihood, obtain for other multifactorial diseases.

The risk of expressing a multifactorial disorder is conditioned by the number of mutant genes involved. The risk is higher for siblings of patients having severe expressions of the disorder. The rate of recurrence of the disorder in first-degree relatives (i.e., parents, siblings, and offspring) of the affected individual. Thus, the risk that the next child will be affected is between 2% and 7%. Similarly, there is the same risk for the next child if the first child is affected. The likelihood that both identical twins will be affected is significantly less than 100%, while the likelihood that both nonidentical twins will be affected is in the range of 20% to 40%. The risk of recurrence of the phenotypic abnormality in subsequent pregnancies is higher than in previous pregnancies. When one child is affected, there is as high as a 7% chance of recurrence, but after two affected siblings, the risk rises to about 9%.





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 Figure 7-9 **Top**, A simplified scheme of normal glycogen metabolism in the liver and skeletal muscles. **Middle**, The enzymes involved in glycogen metabolism. **Bottom**, The consequences of a genetic deficiency in the enzymes

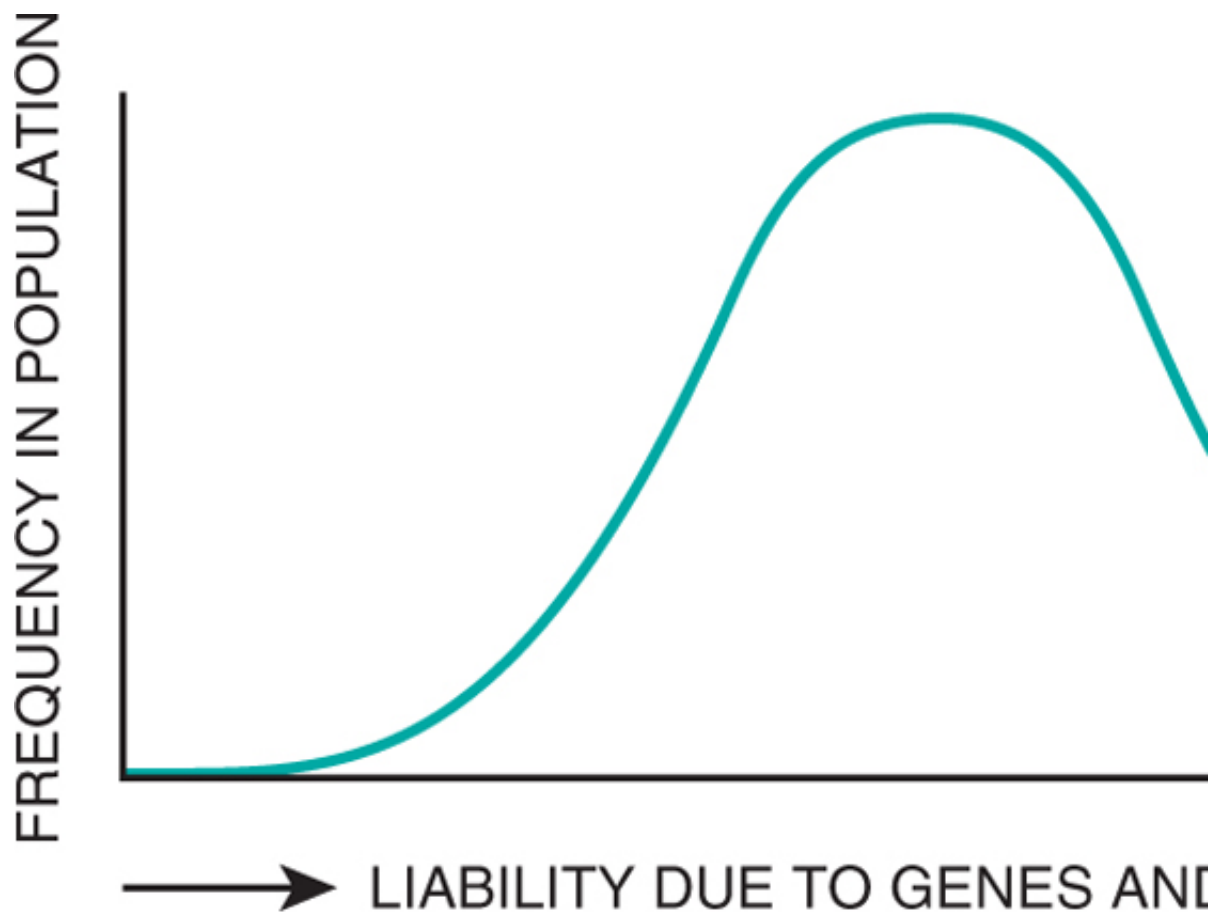


Figure 7-10 Multifactorial inheritance. The continuous distribution of the liability to develop a multifactorial disease in a normal environment. A threshold of liability indicates the limit beyond which disease is expressed. (Adapted from Elsas LJ and Sodeman TM [eds]: Pathologic Physiology: Mechanisms of Disease, 7th ed. Philadelphia, VA: Elsevier, 1996.)

This form of inheritance is believed to underlie such common diseases as diabetes mellitus, hypertension, and certain forms of congenital heart disease, as well as some skeletal abnormalities. Hypertension is an example of multifactorial inheritance. There is good evidence that the level of blood pressure of an individual is under genetic control, apparently governed by many genes of small effect. The pressure levels of the population follow a Gaussian curve of distribution. At some arbitrary level of blood pressure, hypertension is said to exist and is associated with a significant disadvantage to the individual. (Chapter 10.)



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## CYTOGENETIC DISORDERS

Chromosomal abnormalities occur much more frequently than is generally appreciated. It is estimated that 1 in 1000 newborn infants has some form of chromosomal abnormality. The figure is much higher in fetuses. It is estimated that in 50% of first-trimester abortions, the fetus has a chromosomal abnormality. Cytogenetic alterations in the number or structure of chromosomes and may affect autosomes or sex chromosomes.

Before we embark on a discussion of chromosomal aberrations, it should be recalled that a karyotype is a photographic representation of a stained metaphase spread in which the chromosomes are arranged in pairs of homologous chromosomes in order of decreasing length. A variety of techniques for staining chromosomes have been developed. With the G-banding technique, each chromosome set can be seen to possess a distinctive pattern of alternating light and dark bands (Figure 11). The use of banding techniques allows certain identification of each chromosome, as well as the detection of structural changes in the chromosomes (described later).

### *Numeric Abnormalities*

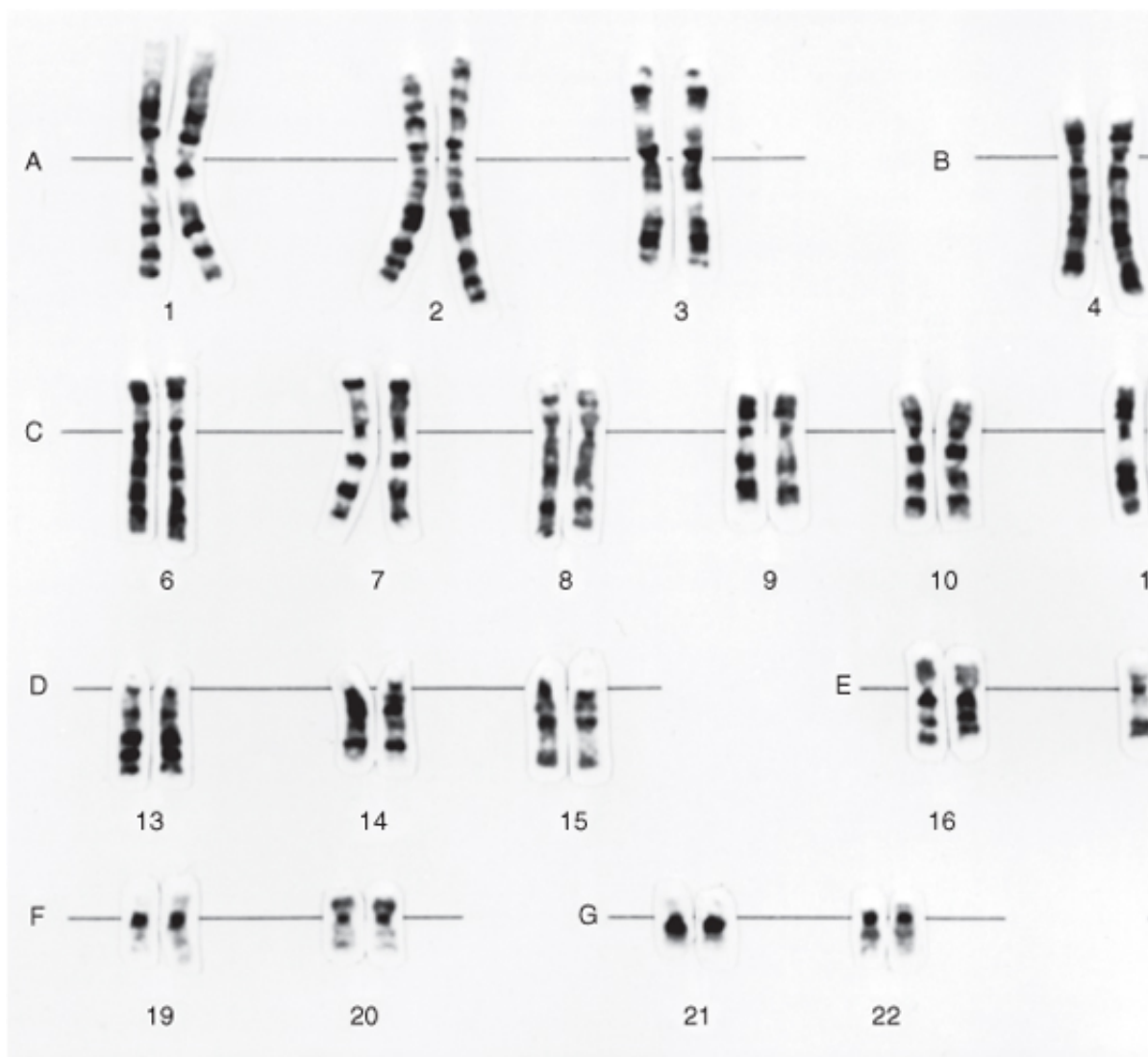


Figure 7-11 Normal male karyotype with G banding. (Courtesy of Dr. Nancy R. Schneider, Department of Pathology, University of Texas Medical School, Dallas, Texas.) Also shown is chromosome 5 in mid-metaphase with G banding to indicate the nomenclature: negative or pale-staining, G bands, and green areas are positive G bands.

In humans, the normal chromosome count is 46 (i.e.,  $2n = 46$ ). Any exact multiple of the haploid  $n$  numbers such as  $3n$  and  $4n$  are called *polyploid*. Polyploidy generally results in a spontaneous ab multiple of  $n$  is called *aneuploid*. The chief cause of aneuploidy is nondisjunction of a homologous division or a failure of sister chromatids to separate during the second meiotic division. The latter division, leading to the production of two aneuploid cells. Failure of pairing of homologous chromosome (anaphase lag) can also lead to aneuploidy. When nondisjunction occurs at the time of meiosis, the chromosome ( $n + 1$ ) or one less chromosome ( $n - 1$ ). Fertilization of such gametes by normal gametes results in trisomic, with an extra chromosome ( $2n + 1$ ), or monosomic ( $2n - 1$ ). Monosomy involving an autosome is usually lethal, whereas trisomies of certain autosomes and monosomy involving sex chromosomes are compatible with life with variable degrees of phenotypic abnormality. *Mosaicism* is a term used to describe the presence of two or more cell lines in the same individual. In the context of chromosome numbers, postzygotic mitotic nondisjunction can result in a trisomic and a monosomic daughter cell; the descendants of these cells would then produce a mosaic. Aneuploidy of sex chromosomes is common, whereas autosomal mosaicism is not.

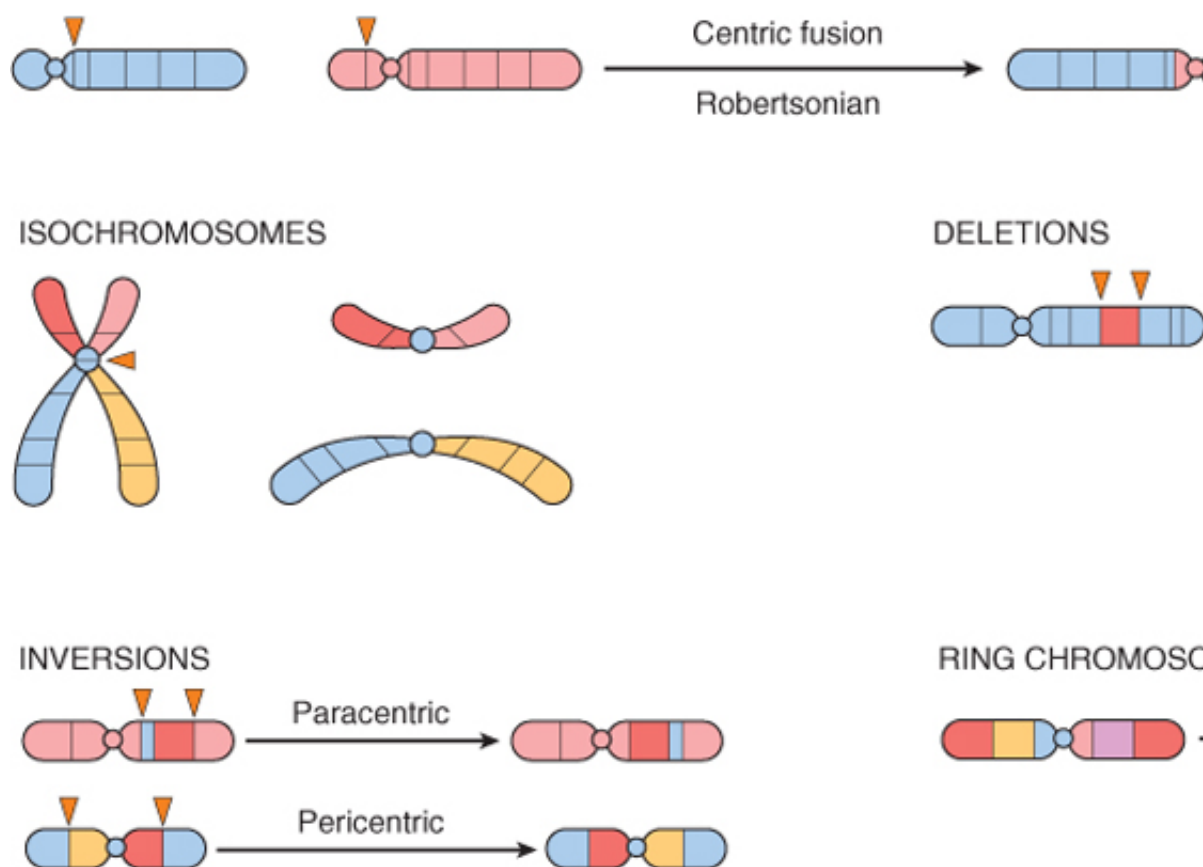
### Structural Abnormalities

Structural changes in the chromosomes usually result from chromosomal breakage followed by loss or gain of segments. Changes are usually designated using a cytogenetic shorthand in which *p* (petit) denotes the short arm. Each arm is then divided into numbered regions (1, 2, 3, and so on) from centromere outward. Bands are numerically ordered (see Fig. 7-11). Thus, 2q34 indicates chromosome 2, long arm, region 3, band 4. Structural rearrangements (Fig. 7-12) are as follows:

*Translocation* implies transfer of a part of one chromosome to another chromosome. The reciprocal exchange of segments between two chromosomes. In genetic shorthand, translocation involves chromosomes in numeric order, for example,  $46,XX,t(2;5)(q31;p14)$ . This would indicate that the long arm (q) of chromosome 2 at region 3, band 1, and the short arm of chromosome 5 at region 1, band 4 are exchanged, the resulting balanced reciprocal translocation (Fig. 7-12) involves the normal number of chromosomes and the full complement of genetic material. However, if unbalanced gametes are formed, resulting in abnormal zygotes. A special pattern of translocation involving acrocentric chromosomes is called *centric fusion type*, or *Robertsonian*, translocation. Typically, the break occurs affecting the short arms of both chromosomes. Transfer of the segments leads to one very large and one very small chromosome (see Fig. 7-12). The short fragments are lost, and the carrier has 45 chromosomes. Acrocentric chromosomes carry highly redundant genes (e.g., ribosomal RNA genes), such as the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and X chromosomes. However, difficulties arise during gametogenesis, resulting in the formation of unbalanced gametes and offspring. *Isoschromosomes* result when the centromere divides horizontally rather than vertically. One of the two resulting chromosomes is then lost, and the remaining arm is duplicated, resulting in a chromosome with two identical arms. The most common isochromosome present in live births involves the long arm of the X chromosome. When fertilization occurs by a gamete that contains a normal X chromosome, there is monosomy for genes on Xq. *Deletion* involves loss of a portion of a chromosome. A single break may delete a segment, with reunion of the proximal and distal segments, may result in loss of an intermedial segment which lacks a centromere, almost never survives, and thus many genes are lost. *Inversions* involve breaks in a chromosome, and the segment reunites after a complete turnaround. A *ring chromosome* results from loss of segments from each end of the chromosome, the arms unite to form a ring.

### TRANSLOCATIONS





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Figure 7-12 Types of chromosomal rearrangements.

Against this background, we can turn first to some general features of chromosomal disorders, for diseases involving changes in the karyotype.

Chromosomal disorders may be associated with absence (deletion, monosomy), excess (trisomy) (translocations) of chromosomes. In general, loss of chromosomal material produces more chromosomal material. Excess chromosomal material may result from a complete chromosome (as in Robertsonian translocation). Imbalances of sex chromosomes (excess or deficiency) produce similar imbalances of autosomes. Sex chromosomal disorders often produce subtle abnormalities. Infertility, a common manifestation, cannot be diagnosed until adolescence. In most cases, *de novo* changes (i.e., parents are normal, and risk of recurrence in siblings is low). An uncorrected principle is exhibited by the translocation form of Down syndrome.

### Cytogenetic Disorders Involving Autosomes

Three autosomal trisomies (21, 18, and 13) and one deletion syndrome (cri du chat syndrome), with short arm of chromosome 5, were the first chromosomal abnormalities identified. More recently, sex chromosome disorders (such as that affecting 22q) have been described. Most of these disorders are quite unusual and should permit ready recognition (Fig. 7-13).

Only trisomy 21 and 22q11.2 deletion occur with sufficient frequency to merit further consideration.

### Trisomy 21 (Down Syndrome)

Down syndrome is the most common of the chromosomal disorders. About 95% of affected persons count is 47. As mentioned earlier, the most common cause of trisomy, and therefore of Down syndrome, is that the parents of such children have a normal karyotype and are normal in all respects. *Maternal age has a strong effect on the incidence of Down syndrome.* It occurs in 1 in 1550 live births in women younger than 20 years, in contrast to 1 in 100 live births in women older than 40 years. The correlation with maternal age suggests that in most cases the meiotic nondisjunction occurred in the mother. Indeed, in 95% of cases the extra chromosome is of maternal origin. The reason for the increased incidence of nondisjunction is not fully understood. No effect of paternal age has been found in those cases in which the extra chromosome is inherited from the father.

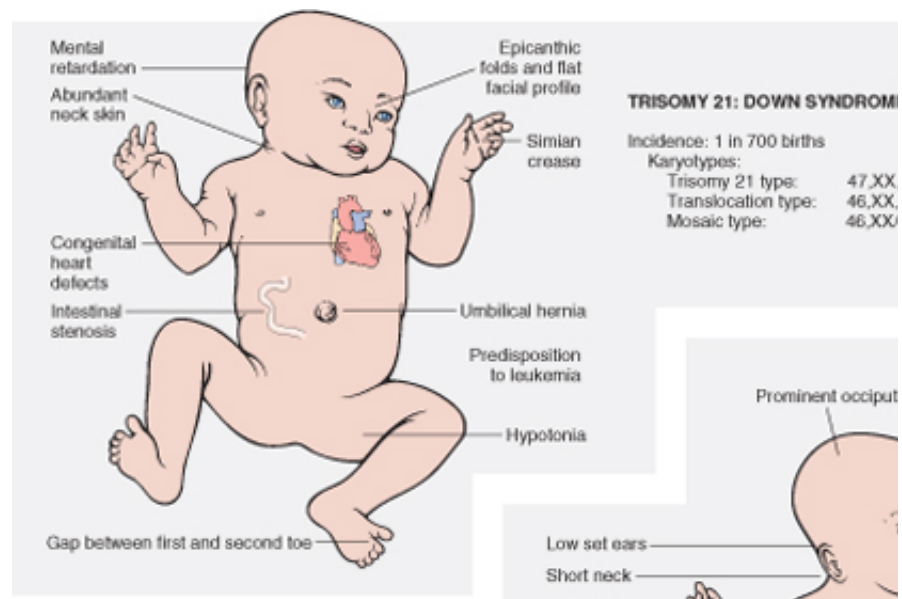
In about 4% of all patients with trisomy 21, the extra chromosomal material is present not as an extra chromosome 21 but as a segment of the long arm of chromosome 21 to chromosome 22 or 14. Such cases are frequently (but not always) inherited from one of the parents, who is most frequently a carrier of a Robertsonian translocation. In these cases, trisomy 21 patients are mosaics, usually having a mixture of 46- and 47-chromosome cells. These cases arise from a nondisjunction of chromosome 21 during an early stage of embryogenesis. Symptoms in such cases are variable and depend on the number of abnormal cells.

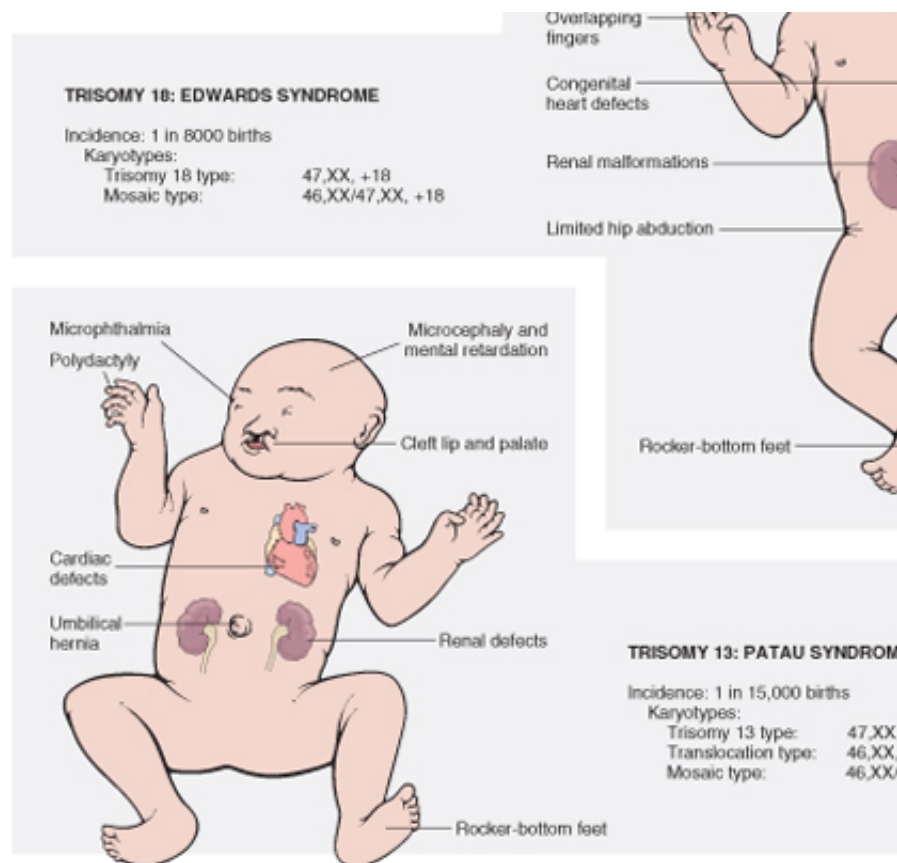
Characteristic clinical features of Down syndrome include *epicanthic folds* and *flat facial profile* (secondary to *mental retardation*). The degree of mental retardation is severe: IQ varies from 25 to 50. (Mental retardation is a term that is being replaced by the term *intellectual disability*.) and quite disabling. Approximately 40% of patients with trisomy 21 have *cardiac malformations*, with a high incidence of deaths in early childhood. *Serious infections* are another important cause of morbidity and mortality. The basis of increased susceptibility to infection is not clearly understood. The chromosomal imbalance *increases the person's risk of developing acute leukemias*, particularly acute megakaryocytic leukemia.

The overall prognosis for individuals with Down syndrome has improved remarkably in the recent years. Currently, the median age at death is 47 years. Most of those who survive into middle age develop the characteristic neurochemical changes of Alzheimer disease (Chapter 24). Many develop frank dementia. The brain is being investigated, with the hope of finding clues to the pathogenesis of Alzheimer disease.

Although the karyotype of Down syndrome has been known for decades, the molecular basis of the disorder is still being investigated. The results of the human genome project indicate that chromosome 21 carries approximately 300 genes. By molecular genetic techniques, a 5-megabase region has been identified as the Down Syndrome Critical Region (DSCR). Within this region, two genes have been identified that regulate the function of NFAT (nuclear factor of activated T-cells), which regulates many target genes in the developmental pathways.

### Chromosome 22q11.2 Deletion Syndrome





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 Figure 7-13 Clinical features and karyotypes of the three most common autosomal

Chromosome 22q11.2 syndrome encompasses a spectrum of disorders that result from a small deletion of chromosome 22. The clinical features of this deletion include congenital heart disease, cleft palate, facial dysmorphism, developmental delay, thymic hypoplasia with impaired T-cell immunity, and hypocalcemia. Previously, these clinical features were believed to represent two different disorders, *velocardiofacial syndrome* and *DiGeorge syndrome*. However, it is now known that both are caused by 22q11.2 deletion. The position of the deletion is responsible for the variable clinical manifestations. When T-cell immunodeficiency is the dominant feature, the patients are said to have *DiGeorge syndrome*, whereas patients with the mild immunodeficiency with pronounced dysmorphism and cardiac defects are said to have *velocardiofacial syndrome*. In addition to these features, patients with 22q11.2 deletion are at a particularly high risk for psychoses such as schizophrenia and bipolar disorders, the mechanisms of which are not fully understood. The affected region of chromosome 22 encodes many genes. Among these, the *TCF7L1* gene is suspected to be responsible, since its loss seems to correlate with the occurrence of *DiGeorge syndrome*.

The diagnosis of this condition may be suspected on clinical grounds but can be established only by fluorescence in situ hybridization (FISH) (see Fig. 7-38B).

## SUMMARY

**Cytogenetic Disorders Involving Autosomes** *Down syndrome* is caused by trisomy 21, most commonly due to trisomy 21, less frequently from translocation of chromosomal material from chromosome 21 to other chromosomes or from mosaicism. Down syndrome has severe mental retardation, flat facial profile, epicanthic folds, malformations of the heart, higher risk of leukemia and infections, and premature development of Alzheimer's disease. Deletion of genes from chromosome 22q11.2 gives rise to malformations of the heart, thymus, and parathyroids. The resulting disorders are recognized as *velocardiofacial syndrome* (thymic hypoplasia with diminished T-cell immunity and parathyroid hypoplasia) and *DiGeorge syndrome*.



(2) *velocardiofacial syndrome* (congenital heart disease affecting outflow tract and developmental delay).

### Cytogenetic Disorders Involving Sex Chromosomes

A number of abnormal karyotypes involving the sex chromosomes, ranging from 45,X to 49,XXXX phenotypically normal males with two and even three Y chromosomes have been identified. Such are encountered with the autosomes. In large part this latitude relates to two factors: (1) lyonization of amount of genetic information carried by the Y chromosome. The consideration of lyonization must be proposed that in females only one X chromosome is genetically active. X inactivation occurs early in conception, and randomly inactivates either the paternal or the maternal X chromosome in each cell of the developing embryo. Once inactivated, the same X chromosome remains genetically neutralized in all descendants. Moreover, all but one X chromosome is inactivated, and so a 48,XXXX female has only one active X chromosome. This explains why normal females do not have a double dose (compared with males) of phenotypic attributes. The Lyon hypothesis also explains why normal females are in reality mosaics, containing two cell populations, one with an active maternal X, the other with an active paternal X. Although essentially accurate, the Lyon hypothesis has been modified under Turner syndrome.

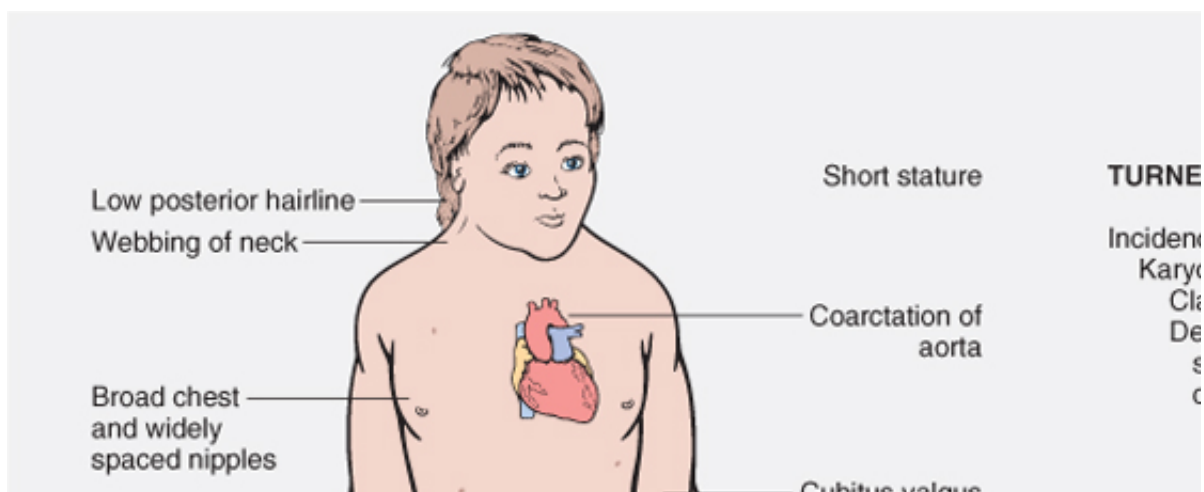
Extra Y chromosomes are readily tolerated because the only information known to be carried on the Y chromosome is for male differentiation. It should be noted that whatever the number of X chromosomes, the presence of a Y chromosome results in a male phenotype. The gene for male differentiation (*SRY*, sex-determining region of Y chromosome) is located on the Y chromosome.

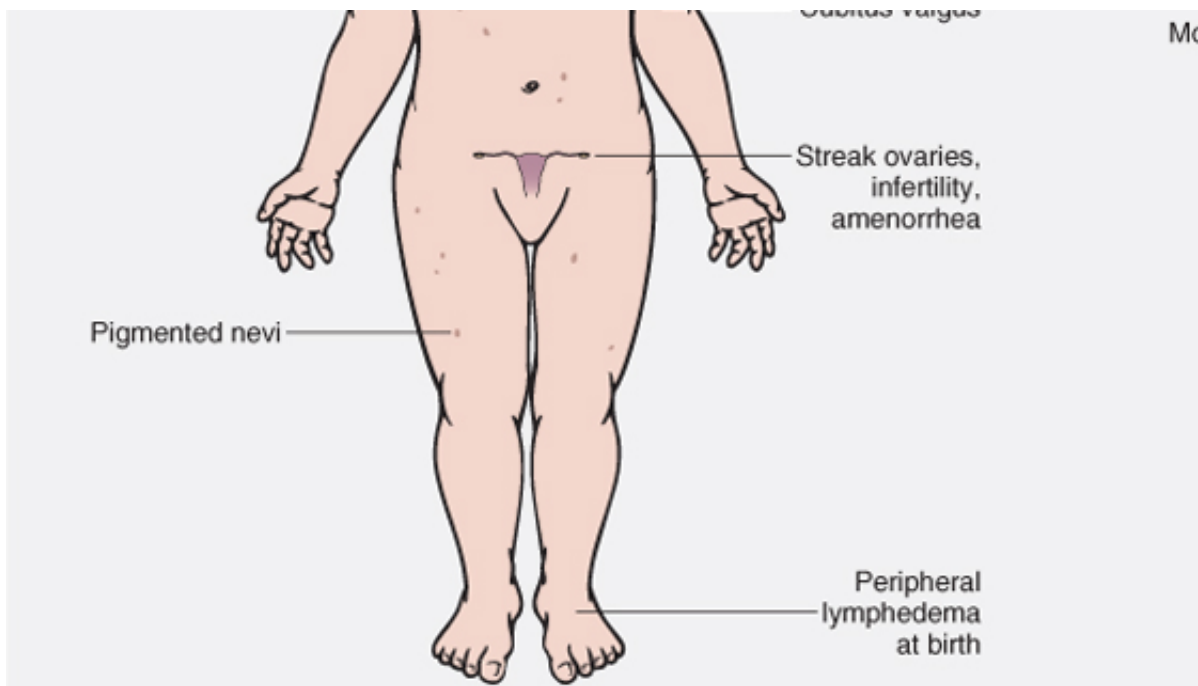
Two disorders—Klinefelter syndrome and Turner syndrome—arising in aberrations of sex chromosomes.

#### **Klinefelter Syndrome**

*This syndrome is best defined as male hypogonadism that develops when there are at least two X chromosomes.* Most patients are 47,XXY. This karyotype results from nondisjunction of sex chromosomes. The extra X chromosome may be of either maternal or paternal origin. Advanced maternal age and a history of miscarriage contribute to the meiotic error resulting in this condition. Approximately 15% of patients show mosaicism, 47,XXY/48,XXXY, and variations on this theme. The presence of a 46,XY line in mosaics is usual in this condition.

Klinefelter syndrome is associated with a wide range of clinical manifestations. In some it may be mild. Most patients have a distinctive body habitus with an *increase in length between the soles and the fingers*, giving the appearance of an elongated body. Also characteristic is eunuchoid body habitus. *Reduced facial hair*, *gynecomastia*, and *osteoporosis* are also frequently noted. The testes are markedly reduced in size, sometimes to only 2 cm in greatest dimension. *Atrophy*, the serum **testosterone<sub>Rx</sub>** levels are lower than normal, and urinary gonadotropin levels are elevated.





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Figure 7-14 Clinical features and karyotypes of Turner syndrome.

*Klinefelter syndrome is the most common cause of hypogonadism in males.* Only rarely are patients mosaics with a large proportion of 46,XY cells. The sterility is due to impaired spermatogenesis, resulting in azoospermia. Histologically, there is hyalinization of tubules, which appear as ghostlike structures. Sertoli cells are prominent, as a result of either hyperplasia or an apparent increase related to loss of tubules. Mental retardation, the degree of intellectual impairment is typically mild and its reduction in intelligence is correlated with the number of extra X chromosomes. Patients with Klinefelter syndrome have an increased risk of developing disorders, such as breast cancer (20 times more common than in normal males), extragonadal germ cell tumors, and autoimmune diseases such as systemic lupus erythematosus.

### **Turner Syndrome**

Turner syndrome, characterized by primary hypogonadism in phenotypic females, results from partial deletion of the X chromosome. With routine cytogenetic methods, the entire X chromosome is missing in the karyotype. These patients are the most severely affected, and the diagnosis can often be made on the basis of clinical features associated with 45,X. Clinical features of Turner syndrome include significant growth retardation (height below third percentile); swelling of the nape of the neck due to distended lymphatic channels (in infancy); webbed neck; low posterior hairline; cubitus valgus (an increase in the carrying angle of the arms); small nipples; high-arched palate; lymphedema of the hands and feet; and a variety of congenital malformations including bicuspid aortic valve, and coarctation of the aorta (Fig. 7-14). Cardiovascular abnormalities are the most common in childhood. In adolescence, affected girls fail to develop normal secondary sex characteristics; the development is minimal, and little pubic hair appears. Most have primary amenorrhea, and morphologically the ovaries are replaced by white streaks of fibrous stroma devoid of follicles. The mental status of these patients is usually normal, but defects in nonverbal, visual-spatial information processing have been noted. Curiously, hypothyroidism is especially common in women with isochromosome Xp. As many as 50% of these develop clinical hypothyroidism. *Short stature and primary amenorrhea should prompt strong suspicion of Turner syndrome.* The diagnosis is confirmed by karyotyping.

Approximately 43% of patients with Turner syndrome are mosaics (one of the cell lines bears a normal 46,XX karyotype). The most common is deletion of the short arm of the X chromosome, resulting in the formation of 46,X,i(X)(q10). The net effect of the associated structural abnormalities is to produce partial monosomy for X-linked genes. Combinations of deletions and mosaicism are reported. It is important to appreciate the karyotypic

syndrome because it is responsible for significant variations in the phenotype. In contrast to the previous hypothesis, *patients with mosaics or have deletion variants may have an almost normal appearance and may present only*

It is pertinent to recall the Lyon hypothesis in the context of Turner syndrome. If only one active X chromosome is present in the development of normal females (as proposed in the Lyon hypothesis), patients with partial or complete monosomy of the X chromosome should not be expected to display the stigmata of Turner syndrome. In view of this inconsistency and other observations, the hypothesis has been modified. It is now known that although one X chromosome is inactivated in all cells during embryonic development, it is reactivated in germ cells before the first meiotic division. Furthermore, it seems that certain X chromosome genes are active in many somatic cells of normal females. Thus, it seems that two copies of some X chromosome genes are active during gametogenesis and somatic development. Some of these genes are beginning to be identified. For example, a gene called short-stature homeobox (*SHOX*), located on Xp22.33, seems to be involved in vertical growth. It is active on both copies of the X chromosome. Homologues of the *SHOX* gene are also found on the Y chromosome. Patients with only one copy of the X chromosome develop normally.

## SUMMARY

**Cytogenetic Disorders Involving Sex Chromosomes** In females one X chromosome is randomly inactivated during development (Lyon hypothesis), and the body is composed of two populations of cells (mosaics). In *Klinefelter syndrome* there are two or more X chromosomes and one Y chromosome as a result of nondisjunction of sex chromosomes. Patients have sterility, reduced body hair, gynecomastia, and eunuchoid body habitus. It is a form of male sterility. In *Turner syndrome* there is partial or complete monosomy of the X chromosome, most commonly due to absence of one X chromosome, but also commonly from mosaicism, or from deletions involving the short arm of the X chromosome. Short stature, webbing of the neck, cubitus valgus, cardiovascular malformations, primary amenorrhea, secondary sex characteristics, and fibrotic ovaries are typical clinical features.





## SINGLE-GENE DISORDERS WITH ATYPICAL PATTERNS OF INHERITANCE

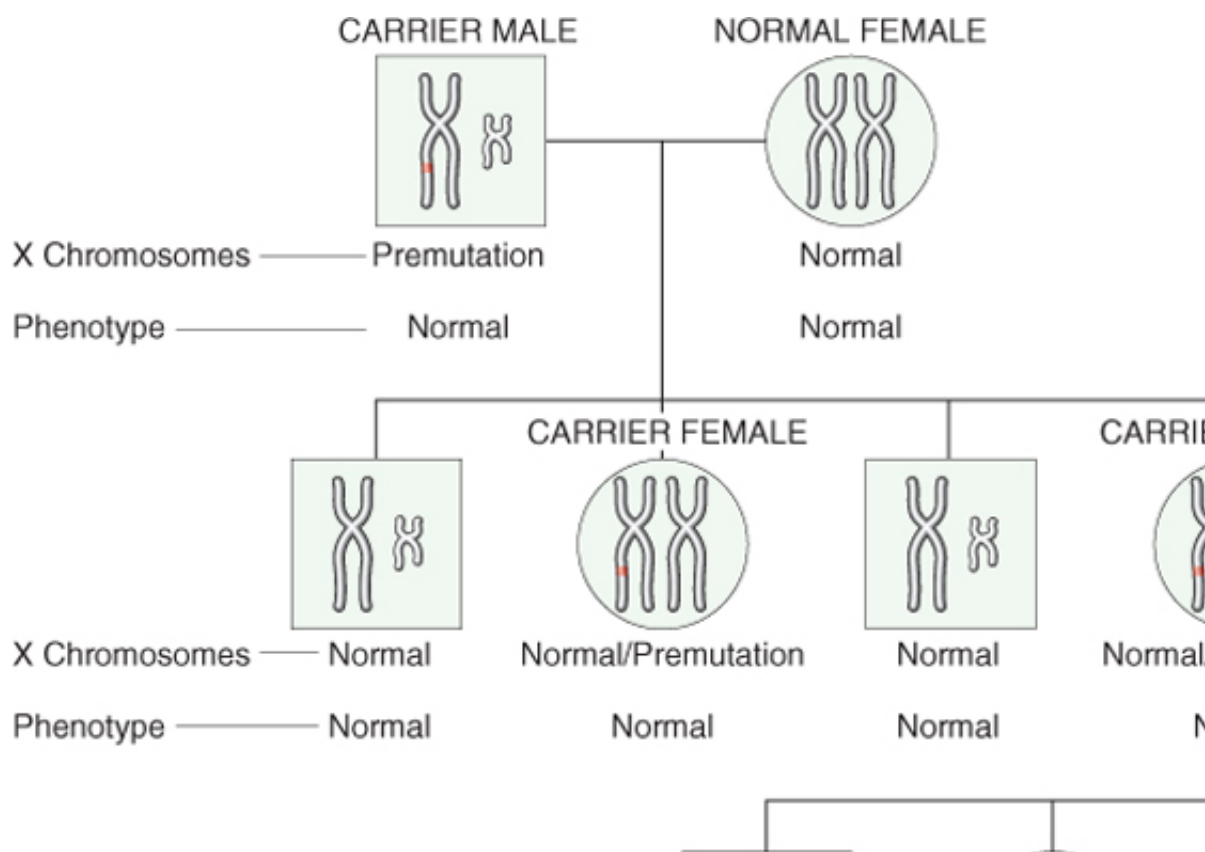
Three groups of diseases resulting from mutations affecting single genes do not follow the Mendelian patterns of inheritance:

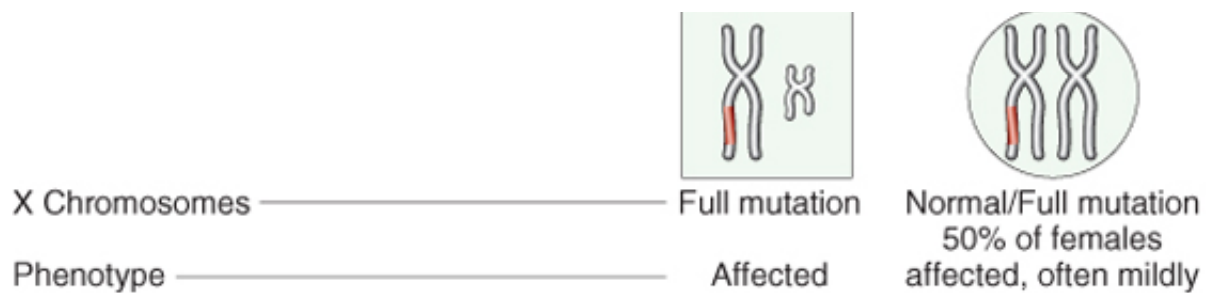
Diseases caused by triplet-repeat mutations  
Diseases caused by mutations in mitochondria  
Genomic imprinting.

### Triplet-Repeat Mutations: Fragile X Syndrome

Fragile X syndrome is the prototype of diseases in which the mutation is characterized by a long run of CAG repeats. Other examples of diseases associated with trinucleotide repeat mutations include Huntington disease. Of about 40 diseases have now been assigned to pathologic expansions of trinucleotide repeats, many are associated with neurodegenerative changes. In each of these conditions, *amplification of specific trinucleotide repeats disrupts its function*. Certain unique features of trinucleotide-repeat mutations, described later, are related to the pattern of inheritance of the associated diseases.

Fragile X syndrome is characterized by mental retardation and an abnormality in the X chromosome called *fragile X*. The cytogenetic alteration, referred to as Fragile X, is induced by a *discontinuity of staining or constriction in the long arm of the X chromosome*. Clinically affected males have mental retardation. They express a characteristic physical phenotype that includes a long face with a large nose and large testicles (*macro-orchidism*). Although characteristic of fragile X syndrome, these abnormalities are subtle. The only distinctive physical abnormality that can be detected in at least 90% of postpubertal males is *macro-orchidism*.

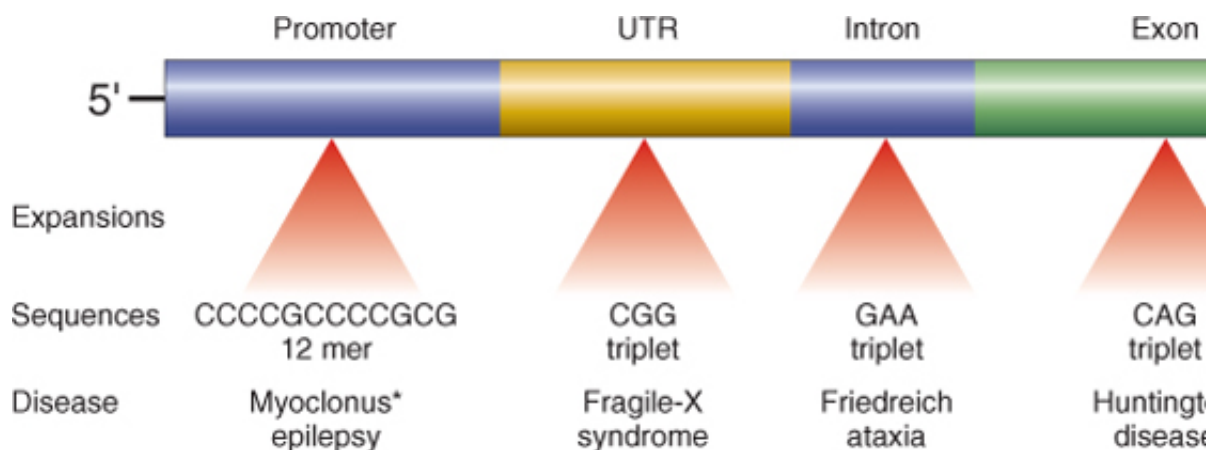




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Figure 7-15 Fragile X pedigree. Note that in the first generation, all sons are normal and all females are carriers. The full mutation expands to full mutation; hence, in the next generation, all males who inherit the X with full mutation are affected. In the next generation, all males who inherit the X with full mutation are affected, and often only mildly. (Based on an original sketch courtesy of Dr. Nancy Schneider, D. Southwestern Medical School, Dallas, Texas.)

Fragile X syndrome results from a mutation in the *FMR1* gene, which maps to Xq27.3. Like all X-linked disorders, it affects males. However, unlike patients with other X-linked recessive disorders, approximately 20% of males with a fragile X mutation may be clinically and cytogenetically normal. These "carrier males" can transmit their phenotypically normal daughters. Another peculiarity is the presence of mental retardation in some affected males. Features have been related to the dynamic nature of the mutation (Fig. 7-15). In the normal population, the *FMR1* gene is small, averaging around 29 CGG repeats, whereas affected individuals have 200 to 4000 repeats. The mutation is believed to arise through an intermediate stage of *premutations* characterized by 52 to 200 CGG repeats. During oogenesis (but not spermatogenesis) the premutations can be converted to full mutations (i.e., expanded to 200+ CGG repeats), which can then be transmitted to both the sons and the daughters of the carrier female (the explanation for why some carrier males are unaffected (they have premutations), and certain carrier females have affected sons (they have full mutations)). Recent studies indicate that premutations are not so benign after all. *Approximately 30% of premutation carriers have premature ovarian failure (before the age of 40 years), and about one-third of premutation carriers develop a neurodegenerative syndrome starting in their sixth decade.* This syndrome, referred to as fragile X-associated tremor/ataxia syndrome (FXTAS), is characterized by intention tremors and cerebellar ataxia and may progress to parkinsonism. However, premutation carriers are milder and occur later in life.



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Figure 7-16 Sites of expansion and the affected sequence in selected diseases caused by nucleotide repeats.

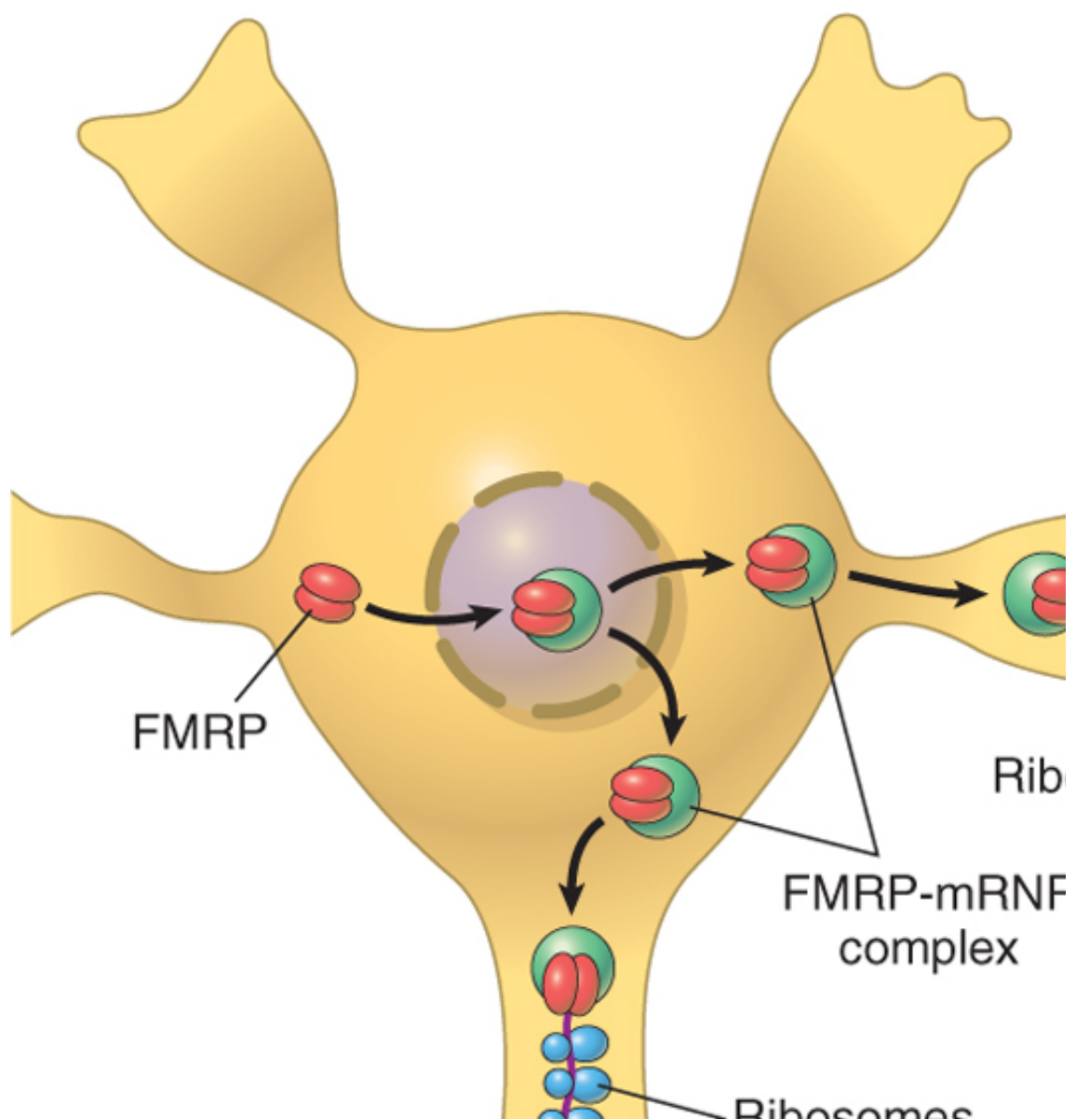
The molecular basis of fragile X syndrome is beginning to be understood. The CGG repeats are located in the 5' UTR of the *FMR1* gene (Fig. 7-16). In patients with this disease, the expanded CGG repeats are hypermethylated, which silences the gene. The product of the *FMR1* gene (FMRP), is widely expressed in normal tissues, but higher levels of transcripts are found in the brain. This suggests that FMRP is an RNA-binding protein that is transported from the cytoplasm to the nucleus. In the brain, FMRP is transported to the axons and dendrites (Fig. 7-17). It is in the synapses that FMRP-mRNA complex

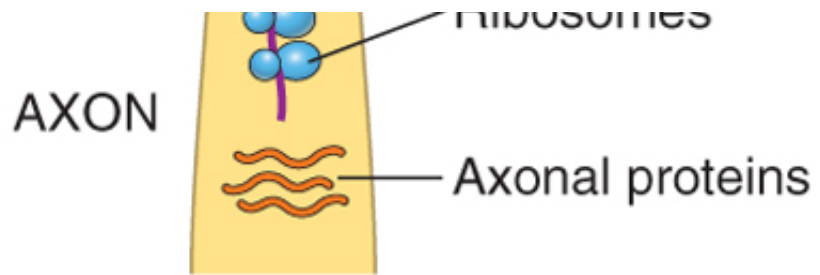


regulating the translation of specific mRNAs. The absence of this finely coordinated "shuttle" function causes fragile X syndrome.

Before closing this discussion, it is appropriate to offer some general comments on other neurodegenerative trinucleotide-repeat expansions.

In all cases, gene functions are altered by an expansion of the repeats, but the precise threshold for conversion to full mutations differs with each disorder. While the expansion in fragile X syndrome is converted to full mutations during spermatogenesis, in disorders such as Huntington disease, premutations are converted to full mutations during oogenesis. Mutations can involve any part of the gene and can be grouped into two broad categories, those that affect noncoding regions (as in fragile X syndrome) or coding regions (as in Huntington disease). When mutations affect noncoding regions, protein synthesis is suppressed (e.g., FMRP). By contrast, mutations involving translated protein regions produce proteins that interfere with function of normal proteins (e.g., Huntington disease). Many of the diseases involving CAG repeats that encode polyglutamine tracts, and the resultant diseases are some of the most severe neurodegenerative diseases, affecting primarily the nervous system. Accumulation of mutant proteins is a common feature of these diseases.





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Figure 7-17 A model for the action of familial mental retardation protein (FMRP) in neurons. (Adapted from Hin P, \ from molecules to neurobehavior. Trends Biochem Sci 28:152, 2003)

## SUMMARY

**Fragile X Syndrome** Pathologic amplification of trinucleotide repeats cause syndrome) or gain-of-function mutations (Huntington disease). Most such m neurodegenerative disorders. Fragile X syndrome results from loss of *FMR1* characterized by mental retardation, macro-orchidism, and abnormal facial i population there are about 29 CGG repeats in the *FMR1* gene. Carrier male permutations with 52 to 200 CGG repeats that can expand to 4000 repeats oogenesis. When full mutations are transmitted to progeny, fragile X syndro

## Diseases Caused By Mutations in Mitochondrial Genes

Mitochondria contain several genes that encode enzymes involved in oxidative phosphorylation. Unlike that of nuclear DNA in that the former is associated with *maternal inheritance*. The reason for mitochondria within their abundant cytoplasm, whereas spermatozoa contain few, if any, mitochondria complement of the zygote is derived entirely from the ovum. Thus, mothers transmit mitochondria and female; however, daughters but not sons transmit the DNA further to their progeny.

Diseases caused by mutations in mitochondrial genes are rare. Because mitochondrial DNA encodes oxidative phosphorylation, diseases caused by mutations in such genes affect organs most dependent on oxidative phosphorylation (e.g., muscle, heart, brain). Leber hereditary optic neuropathy is the prototypical disorder in this group. It manifests itself as progressive bilateral loss of central vision that leads in due course to blindness.

## Genomic Imprinting: Prader-Willi and Angelman Syndromes

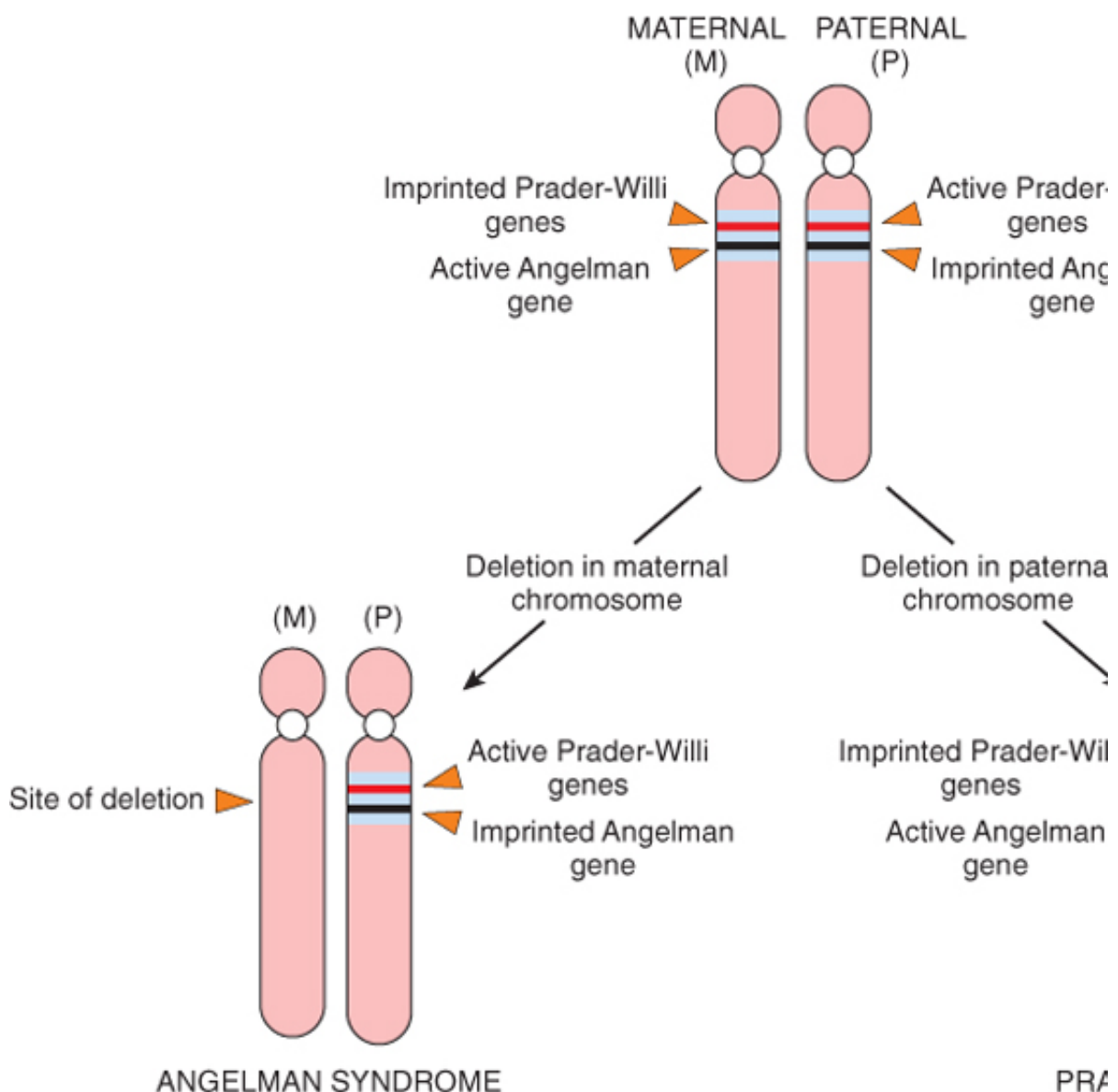
All humans inherit two copies of each gene, carried on homologous maternal and paternal chromosomes. In most cases, there is no difference between normal homologous genes derived from the mother or the father. However, it has now been established that with respect to some genes, functional differences exist between the two alleles. These differences arise from an epigenetic process called *genomic imprinting*, whereby certain genes are silenced during paternal and maternal gametogenesis. Thus, *maternal imprinting* refers to transcriptional silencing of the paternal allele, while *paternal imprinting* implies that the paternal allele is inactivated. Imprinting occurs in ovum or sperm, and thus is not present in somatic cells derived from the zygote.

Genomic imprinting is best illustrated by considering two uncommon genetic disorders: Prader-Willi and Angelman syndromes.

**Prader-Willi syndrome** is characterized by mental retardation, short stature, hypotonia, obesity, and hypogonadism. In 60% to 75% of cases, an interstitial deletion of band q12 in the long arm of chromosome 15 [i.e., 15q11-q13] is detected. In many patients without a detectable cytogenetic abnormality, FISH analysis reveals smaller deletions. *In all cases the deletion affects the paternally derived chromosome 15.* In contrast with Prader-Willi syndrome, phenotypically distinct **Angelman syndrome** are born with a deletion of the same chromosomal region. Children with Angelman syndrome are also mentally retarded, but in addition they present with ataxic gait, inappropriate laughter, and hyperactivity. Because of the laughter and ataxia, this syndrome is also called the *happy puppet syndrome*. A child with Angelman syndrome clearly demonstrates the "parent-of-origin" effects on gene function. If all the paternal and maternal

were expressed in an identical fashion, clinical features resulting from these deletions would be expected to be independent of the parental origin of chromosome 15.

The molecular basis of these two syndromes can be understood in the context of imprinting (Fig. 7-18). The maternal chromosome 15q12 is imprinted (and hence silenced), and thus the only functional allele of the Prader-Willi gene is on the paternal chromosome. When these are lost as a result of a deletion (in the paternal chromosome), the patient has Prader-Willi syndrome. Conversely, a distinct gene that also maps to the same region of chromosome 15 is imprinted on the paternal chromosome, and the only functional allele of the gene is normally active on the maternally derived allele of the gene. Deletion of this maternal gene on chromosome 15 results in Angelman syndrome. Molecular studies of cytogenetically normal patients with Prader-Willi syndrome have revealed that the structurally normal chromosome 15s are derived from the mother. Inheritance of both chromosomes 15 from the mother is termed uniparental disomy. The net effect is the same (i.e., the patient does not have a functional set of genes on chromosome 15). Angelman syndrome, as might be expected, can also result from uniparental disomy.



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Figure 7-18 Genetics of Angelman and Prader-Willi syndromes.

The Angelman syndrome gene (imprinted on paternal chromosome) is now known to encode a protein that is involved in the regulation of gene expression.

the Angelman syndrome gene (imprinted on paternal chromosome), is not involved in the proteasome proteolytic pathway ([Chapter 1](#)). This gene, called, somewhat laboriously, *UBE3A*, is active in specific regions of the normal brain. In Angelman syndrome, *UBE3A* is not expressed in the affected neurologic disorder. Prader-Willi syndrome, unlike Angelman syndrome, is most likely caused by deletions of 15q11 and q13. These genes are still being fully characterized.

## SUMMARY

**Genomic Imprinting** Imprinting involves transcriptional silencing of the paternal or maternal allele of certain genes during gametogenesis. For such genes only one functional allele is active. Loss of the functional allele (not imprinted) by deletions gives rise to disease. Prader-Willi syndrome results from deletion of paternal chromosome 15q12 and is characterized by hypotonia, hypogonadism, and obesity. *Angelman syndrome* results from deletion of maternal chromosome 15q12 and is characterized by mental retardation, ataxia, and frequent laughter.



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## PEDIATRIC DISEASES

As mentioned earlier and illustrated by several examples, many diseases of infancy and childhood are of genetic origin. Others, though not genetic, either are unique to children or take distinctive forms in this stage of life and so merit the designation *pediatric diseases*. During each stage of development, infants and children are prey to a somewhat different group of diseases ([Table 7-8](#)). Clearly, diseases of infancy (i.e., the first year of life) pose the highest risk of mortality. During this phase, the neonatal period (the first 4 weeks of life) is unquestionably the most hazardous time.

**Table 7-8. Causes of Death by Age**

<b>Causes*</b>	<b>Rate<sup>†</sup></b>
<b>Under 1 Year: All Causes</b>	<b>727.4</b>
Congenital malformations, deformations, and chromosomal anomalies	
Disorders related to short gestation and low birth weight	
Sudden infant death syndrome (SIDS)	
Newborn affected by maternal complications of pregnancy	
Newborn affected by complications of placenta, cord, and membranes	
Respiratory distress of newborn	
Accidents (unintentional injuries)	
Bacterial sepsis of newborn	
Intrauterine hypoxia and birth asphyxia	
Diseases of the circulatory system	
All other causes	
<b>1-4 Years: All Causes</b>	<b>32.6</b>
Accidents and adverse effects	
Congenital malformations, deformations, chromosomal abnormalities	
Malignant neoplasms	
Homicide and legal intervention	
Disease of the heart‡	
Influenza and pneumonia	
<b>5-14 Years: All Causes</b>	<b>18.5</b>
Accidents and adverse effects	
Malignant neoplasms	
Homicide and legal intervention	
Congenital malformations, deformations, chromosomal abnormalities	
Suicide	
Diseases of the heart	
<b>15-24 Years: All Causes</b>	<b>80.7</b>
Accident and adverse effects	
Homicide	
Suicide	
Malignant neoplasms	
Diseases of the heart	

\*Causes are listed in decreasing order of frequency.



\*Causes are listed in decreasing order of frequency.

†Rates are expressed per 100,000 population.

‡Excludes congenital heart disease. All causes and rates are preliminary 2000 statistics.

From Minino AM, Smith BL: Deaths: Preliminary data for 2000. National Vital Statistics Report, 49:12, 2001.

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Once the infant survives the first year of life, the outlook brightens considerably. However, it is sobering to note that between 1 year and 15 years of age, injuries resulting from accidents are the leading cause of death. Not all conditions listed in [Table 7-8](#) are described in this chapter, but only a select few that are most common. Although general principles of neoplastic disease and specific tumors are discussed elsewhere, a few tumors of children are described here to highlight the differences between pediatric and adult neoplasms.



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## CONGENITAL ANOMALIES

Congenital anomalies are structural defects that are present at birth, although some, such as cancer, become clinically apparent until years later. As will be evident from the ensuing discussion, the teratogenic basis for birth defects. It is estimated that about 3% of newborns have a major anomaly, of cosmetic or functional significance. As indicated in Table 7-8, congenital anomalies are an important cause of illness, disability, and death throughout the early years of life.



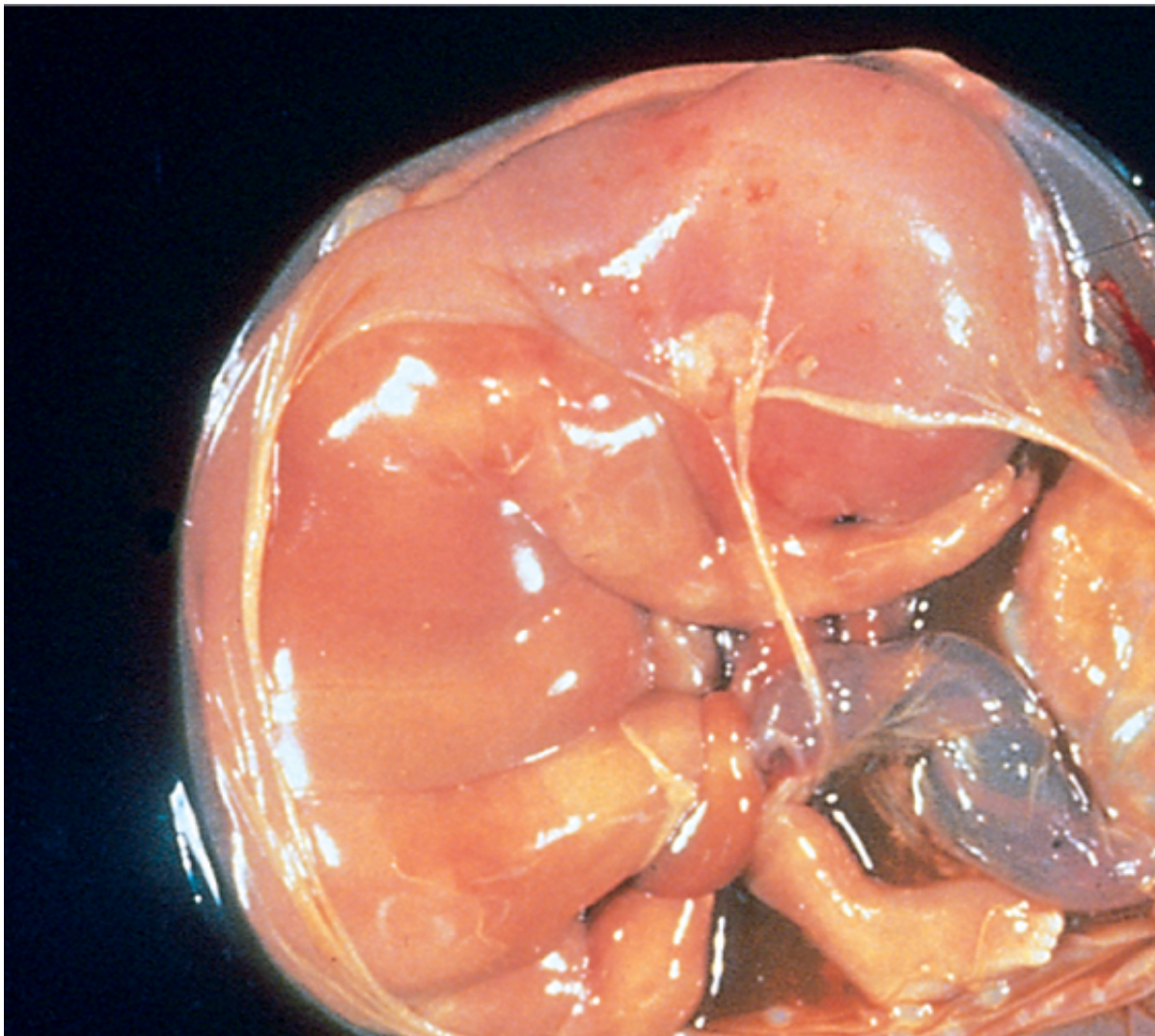
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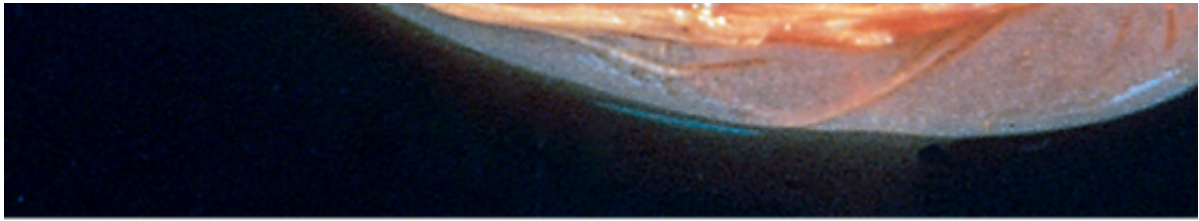
Figure 7-19 Human malformations can range in severity from the incidental to the lethal. **A**, Polydactyly (one or more extra digits) have little functional consequence when they occur in isolation. **B**, Similarly, cleft lip, with or without associated cleft palate, is an isolated anomaly; in this case, however, the child had an underlying malformation syndrome (trisomy 13) and died. **C**, Stillbirth representing a severe and essentially lethal malformation, in which the midface structures are fused or ill-developed. This dysmorphism is associated with severe internal anomalies such as maldevelopment of the brain and cardiac defects. **Quinton. B**, Courtesy of Dr. Beverly Rogers, Department of Pathology, University of Texas Southwest

Before the etiology and pathogenesis of congenital anomalies are described, it is essential to define the terms used to describe errors in morphogenesis.

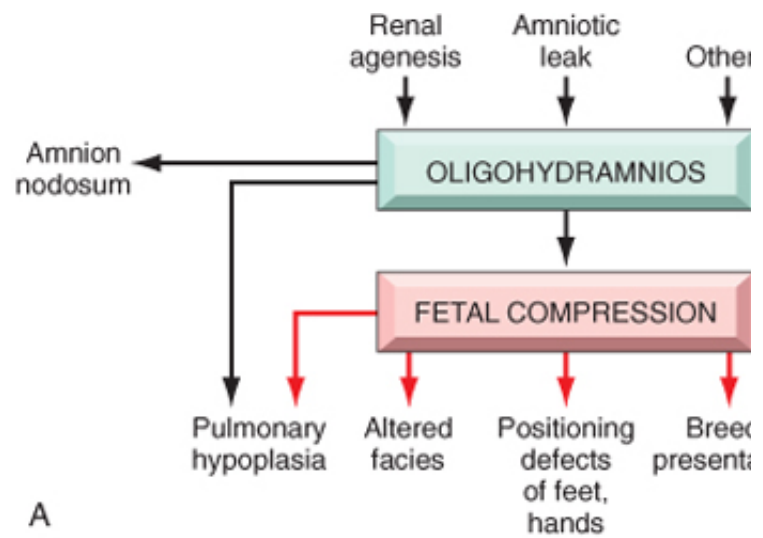
**Malformations** represent primary errors of morphogenesis. In other words, there is an intrinsic error in the development of a body part. Malformations are usually multifactorial rather than the result of a single gene or chromosomal abnormality. In some, such as congenital heart diseases, single body systems may be involved; in others, malformations involving many organs and tissues may coexist (Fig. 7-19). **Disruptions** result from the loss of a part of a body region that was previously normal in development; thus, in contrast to malformations, disruptions are the result of a disturbance in morphogenesis. **Amniotic bands**, denoting rupture of amnion with resultant fibrous bands that may compress, or attach to parts of the developing fetus, are the classic example of a disruption. **Deformations**, like disruptions, are not heritable anomalies and do not recur in subsequent pregnancies. **Deformations**, like disruptions, also represent an extrinsic error of morphogenesis. Deformations are common problems, affecting a wide variety of body parts. Fundamental to the pathogenesis of deformations is localized or generalized

various degrees. Fundamental to the pathogenesis of deformations is localized or general abnormal biomechanical forces, leading eventually to a variety of structural abnormalities. A major cause of deformations is uterine constraint. Between the 35th and 38th weeks of gestation, rapid increase in the growth of the uterus, and the relative amount of amniotic fluid (which normally acts as a cushion), the normal fetus is subjected to some form of uterine constraint. However, several variable factors can lead to compression of the fetus, including maternal conditions such as first pregnancy, small uterus, and uterine leiomyomas. Causes relating to the fetus, such as multiple fetuses, oligohydramnios, and a large fetus, are also involved. *Sequence* refers to multiple congenital anomalies that result from *secondary effects* of a primary defect. The initiating event may be a malformation, deformation, or disruption. An example is the (or Potter) sequence (Fig. 7-21A). Oligohydramnios, denoting decreased amniotic fluid, may be caused by maternal, placental, or fetal abnormalities. Chronic leakage of amniotic fluid due to rupture of the membranes, insufficiency resulting from maternal hypertension or severe toxemia, and renal agenesis (in which the kidneys are a constituent of amniotic fluid) are all causes of oligohydramnios. The fetal compression associated with oligohydramnios results in a classic phenotype in the newborn infant, including flattened facies and position of the feet (Fig. 7-21B). The hips may be dislocated. Growth of the chest wall and the contained internal organs is restricted to such an extent that survival is not possible. If the embryologic connection between these defects is recognized, a sequence may be mistaken for a malformation syndrome. *Malformation syndrome* refers to defects that cannot be explained on the basis of a single localizing initiating error in morphogenesis, but rather from a single causative condition (e.g., viral infection or a specific chromosomal abnormality affecting multiple tissues).





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 Figure 7-20 Disruptions occur in a normally developing organ because of an extrinsic abnormality that interferes w  
 frequent cause of disruptions. In the illustrated example, note the placenta at the right of the diagram and the band  
 amniotic sac to encircle the leg of the fetus. (Courtesy of Dr. Theonia Boyd, Children's Hospital of I







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Figure 7-21 **A**, Pathogenesis of the oligohydramnios (Potter) sequence. **B**, Infant with oligohydramnios (Potter) deformed foot (talipes equinovarus).

In addition to the global definitions listed previously, some general terms are applied to organ-specific malformations. *Aplasia* refers to the complete absence of an organ or its anlage, whereas *hypoplasia* is used to indicate underdevelopment of an organ. *Atresia* describes the absence of an opening, usually of a hollow organ or bile ducts.

### Etiology

Known causes of errors in human malformations can be grouped into three major categories: *genetic* (Table 7-9). *Almost half have no recognized cause.*

**Table 7-9. Causes of Congenital Malformations in Humans**

Cause	Malformed Live Births per 1,000
<b>Genetic</b>	
Chromosomal aberrations	10-15
Mendelian inheritance	2-10
<b>Environmental</b>	
Maternal/placental infections	2-3
Rubella	
Toxoplasmosis	
Syphilis	
Cytomegalovirus infection	
Human immunodeficiency virus infection	
Maternal disease states	6-8
Diabetes	
Phenylketonuria	
Endocrinopathies	
Drugs and chemicals	~1
Alcohol	
Folic acid antagonists	
Androgens	
Phenytoin	
Thalidomide	
Warfarin	
13- <i>cis</i> -Retinoic acid	
Others	
Irradiation	~1
<b>Multifactorial</b>	<b>20-25</b>
<b>Unknown</b>	<b>40-60</b>

Adapted from Stevenson RE, et al. (eds): Human Malformations and Related Anomalies. New York, Oxford University Press, 1993

**Genetic causes** of malformations include all of the previously discussed mechanisms of genetic disorders. Examples include Down syndrome and Klinefelter syndrome. Most chromosomal disorders arise during gametogenesis and hence are not



characterized by mendelian inheritance, may underlie major malformations. For example, holoprosencephaly, a developmental defect of the forebrain and midface in humans (see [Chapter 23](#)); mutations of *sonic hedgehog*, have been reported in a subset of holoprosencephaly patients. Similarly, mutations in *GLI3*, have been reported in patients with anomalies of digits, either conjoined digits (*polydactyly*).

*Environmental influences*, such as viral infections, drugs, and irradiation to which the mother was exposed, can cause fetal malformations (the appellation of "malformation" is loosely used in this context, since technical terms are *disruptions*). Among the viral infections listed in [Table 7-9](#), rubella was a major scourge of the 19th century. Maternal rubella and the resultant *rubella embryopathy* have been virtually eliminated in developed countries. A variety of drugs and chemicals have been suspected to be teratogenic, but perhaps less than 1% by these agents. The list includes *thalidomide*<sup>®</sup>, alcohol, anticonvulsants, warfarin (oral anticoagulant used in the treatment of severe acne. For example, *thalidomide*<sup>®</sup>, once used as a tranquilizer in Europe, due to its anti-angiogenic properties, causes an extremely high incidence (50% to 80%) of limb malformations. *Thalidomide*<sup>®</sup> is no longer used as a tranquilizer today, is an important environmental teratogen. Affected infants show prenatal and postnatal anomalies (microcephaly, short palpebral fissures, maxillary hypoplasia), and psychomotor disturbance. *Fetal alcohol syndrome*. While cigarette smoke-derived *nicotine*<sup>®</sup> has not been convincingly demonstrated to cause a high incidence of spontaneous abortions, premature labor, and placental abnormalities in pregnant women, exposure to cigarette smoke often have a low birth weight and may be prone to the sudden infant death syndrome. *In liquor* exposure *nicotine*<sup>®</sup> exposure *altogether during pregnancy*. Among maternal conditions listed in [Table 7-9](#), *diabetes mellitus*, despite advances in antenatal obstetric monitoring and *glucose*<sup>®</sup> control, the incidence of major malformations in infants of mothers stands between 6% and 10% in most series. Maternal hyperglycemia-induced fetal hyperglycemia (organomegaly and increased body fat and muscle mass); cardiac anomalies, neural tube defects (spina bifida) are of the major anomalies seen in *diabetic embryopathy*.

*Multifactorial inheritance*, which implies the interaction of environmental influences with two or more common genetic causes of congenital malformations. Included in this category are some relatively common malformations such as cleft lip and palate and neural tube defects. The importance of environmental contributions to multifactorial inheritance is demonstrated by the dramatic reduction of the incidence of neural tube defects by periconceptional intake of *folic acid*<sup>®</sup>. The mode of transmission of multifactorial disorders were described earlier in this chapter.

### *Pathogenesis*

The pathogenesis of congenital malformations is complex and still poorly understood, but two important developmental pathways are relevant regardless of the etiologic agent:

*The timing of the prenatal insult has an important impact on both the occurrence and the type of malformation.* Intrauterine development of humans can be divided into two phases: the embryonic period, which terminates at birth. In the early embryonic period (the first trimester), an injurious agent damages either enough cells to cause death and abortion, or only a few cells recover without developing defects. Between the 3rd and 9th weeks, the embryo is extremely sensitive; during this period, sensitivity is between the fourth and fifth weeks. It is during this period that the germ cell layers are formed. The fetal period that follows organogenesis is marked chiefly by further growth. The fetus is greatly reduced susceptibility to teratogenic agents. Instead, the fetus is susceptible to growth retardation and organ dysfunction. It is therefore possible for the same teratogenic agent to produce different effects in different stages of gestation. For example, viral infections such as rubella produce disruption of the development of the heart and other organs later during pregnancy, the result of viral infection is usually tissue injury accompanied by inflammation (see section below). The approximate timing of the insult can be gauged from the pattern of defects. Thus, a ventricular septal defect resulting from exposure to a teratogen must have occurred because the ventricular septum closes at this time. *Genes that regulate morphogenesis* Malformations caused by single-gene mutations in causing human malformations is becoming increasingly evident. The function of genes controlling developmental events is likely to be affected by teratogens as homeobox (*HOX*) genes, which regulate transcription of several other genes, and in experimental animals, misexpression are known to produce malformations. For example, infants born to mothers treated with *retinoic acid* develop *retinoic acid embryopathy*, including CNS, cardiac, and craniofacial defects. In ani

reproducible changes in *HOX* gene expression and causes a wide range of structural congenital anomalies seen in retinoic acid embryopathy. A variety of other teratogens (e.g., the anticonvulsant sodium valproate) also cause effects through disruption of *HOX* gene expression.

## SUMMARY

**Congenital Anomalies** Congenital anomalies result from intrinsic abnormalities as well as extrinsic disturbances (deformations, disruptions). Congenital anomalies can be genetic (chromosomal abnormalities, gene mutations), environmental (infectious, teratogens), or multifactorial causes. The timing of the in utero insult has profound influence on the type of congenital anomalies, with earlier events usually demonstrating greater impact.



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## PERINATAL INFECTIONS

Infections of the fetus and neonate may be acquired transcervically (ascending infections) or transplacentally (hematologic infections).

Transcervical, or *ascending, infections* involve spread of infection from the cervicovaginal canal and may be acquired in utero or during birth. Most bacterial infections (e.g.,  $\alpha$ -hemolytic streptococcal infection) and a few viral infections (e.g., herpes simplex) are acquired in this manner. In general, the fetus acquires the infection by "inhaling" infected amniotic fluid into the lungs or by passing through an infected birth canal during delivery. Fetal infection is usually associated with inflammation of the placental membranes (chorioamnionitis) and inflammation of the umbilical cord (funisitis). This mode of spread usually gives rise to pneumonia and, in severe cases, to sepsis and meningitis. Transplacental infections gain access to the fetal bloodstream by crossing the placenta via the chorionic villi, and may occur at any time during gestation or occasionally, as may be the case with hepatitis B and human immunodeficiency virus, at the time of delivery via maternal-to-fetal transfusion. Most parasitic (e.g., toxoplasma, malaria) and viral infections, and a few bacterial infections (i.e., *Listeria*, *Treponema*) demonstrate this mode of hematogenous transmission. The clinical manifestations of these infections are highly variable, depending largely on the gestational timing and microorganism involved. The most important transplacental infections can be conveniently remembered by the acronym *TORCH*. The elements of the TORCH complex are the following: *Toxoplasma* (T), rubella virus (R), cytomegalovirus (C), herpesvirus (H), and any of a number of other (O) microbes such as *Treponema pallidum*. These agents are grouped together because they may evoke similar clinical and pathologic manifestations. TORCH infections occurring early in gestation may cause chronic sequela in the child, including growth restriction, mental retardation, cataracts, and congenital cardiac anomalies, while infections later in pregnancy result primarily in tissue injury accompanied by inflammation (encephalitis, chorioretinitis, hepatosplenomegaly, pneumonia, and myocarditis).





## PREMATURITY AND FETAL GROWTH RESTRICTION

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Prematurity is the second most common cause of neonatal mortality (second only to congenital anomalies), and is defined by a gestational age less than 37 weeks. As might be expected, infants born before completion of gestation also weigh less than normal (<2500 gm). The major risk factors for prematurity include premature rupture of membranes; intrauterine infection leading to inflammation of the placental membranes (chorioamnionitis); structural abnormalities of the uterus, cervix, and placenta; and multiple gestation (e.g., twin pregnancy). It is well established that children born before completion of the full period of gestation are subject to a higher incidence of morbidity and mortality than are full-term infants. The immaturity of organ systems in preterm infants makes them especially vulnerable to several complications discussed below, including:

Hyaline membrane disease (respiratory distress syndrome). Necrotizing enterocolitis. Intraventricular and germinal matrix hemorrhage ([Chapter 23](#)).

Although preterm infants have low birth weights, it is usually appropriate once adjusted for their gestational age. In contrast, as many as one-third of infants who weigh less than 2500 gm are born at term and are therefore undergrown rather than immature. These small-for-gestational-age (SGA) infants suffer from fetal growth restriction. Fetal growth restriction may result from fetal, maternal, or placental abnormalities, although in many cases the specific cause is unknown.

*Fetal factors* are those that intrinsically reduce growth potential of the fetus despite an adequate supply of nutrients from the mother. Prominent among such fetal conditions are *chromosomal disorders*, *congenital anomalies*, and *congenital infections*. Chromosomal abnormalities may be detected in as many as 17% of fetuses sampled for fetal growth restriction and in as many as 66% of fetuses with documented ultrasonographic malformations. *Fetal infection* should be considered in all growth-restricted neonates, with the TORCH group of infections (*see above*) being a common cause. When the causation is intrinsic to the fetus, growth retardation is *symmetric* (i.e., affects all organ systems equally). *Placental causes* include any factor that compromises the uteroplacental supply line. This may result from placenta previa (low implantation of the placenta), placental abruption (separation of placenta from the decidua by a retroplacental clot), or placental infarction. With placental (and maternal) causes of growth restriction, the growth retardation is *asymmetric* (i.e., the brain is spared relative to visceral organs such as the liver). *Maternal factors* are by far the most common cause of the growth deficit in SGA infants. These include vascular diseases such as preeclampsia ("toxemia of pregnancy") ([Chapter 19](#)) and chronic hypertension. The list of other maternal conditions associated with growth-restricted infants is long, but some of the avoidable influences are maternal narcotic abuse, alcohol intake, and heavy cigarette smoking (recall that many of these same causes are also involved in the pathogenesis of congenital anomalies). Drugs causing fetal growth restriction similarly include teratogens, such as the commonly administered anticonvulsant [phenytoin](#)<sup>®</sup> (Dilantin), as well as nonteratogenic agents. Maternal malnutrition (in particular, prolonged hypoglycemia) may also affect fetal growth, but the association between growth-restricted infants and the nutritional status of the mother is complex.

The growth-restricted infant is handicapped not only in the perinatal period but also in

childhood and adult life. These individuals are at increased risk for cerebral dysfunction, learning disabilities, and sensory (i.e., visual, hearing) impairment.



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## RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN

There are many causes of respiratory distress in the newborn, including excessive sedation of the aspiration of blood or amniotic fluid, and intrauterine hypoxia brought about by coiling of the umbilical cord. The most common cause is respiratory distress syndrome (RDS), also known as *hyaline membrane disease*. "membranes" in the peripheral air spaces of infants who succumb to this condition. Approximately 10,000 cases per year, and in 2002, a little more than 1000 deaths were ascribed to this disease. The tremendous expense of management of RDS can be estimated by recalling that in the 1960s there were more than 25,000

### *Pathogenesis*

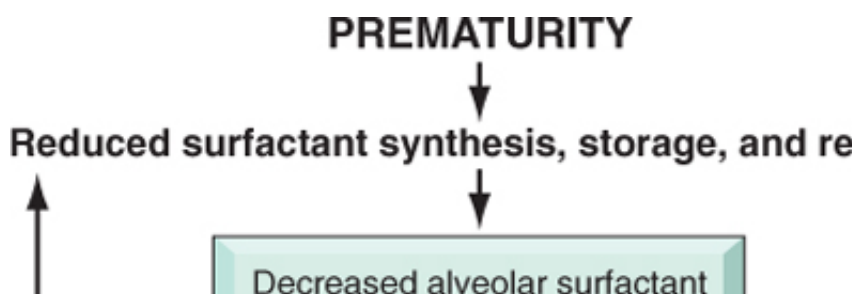
*RDS is basically a disease of premature infants.* It occurs in about 60% of infants born at less than 32 weeks of gestation, and fewer than 5% of those born after 37 weeks. Risk factors and influences are *maternal diabetes*, *cesarean section* before the onset of labor, and *twin gestation*.

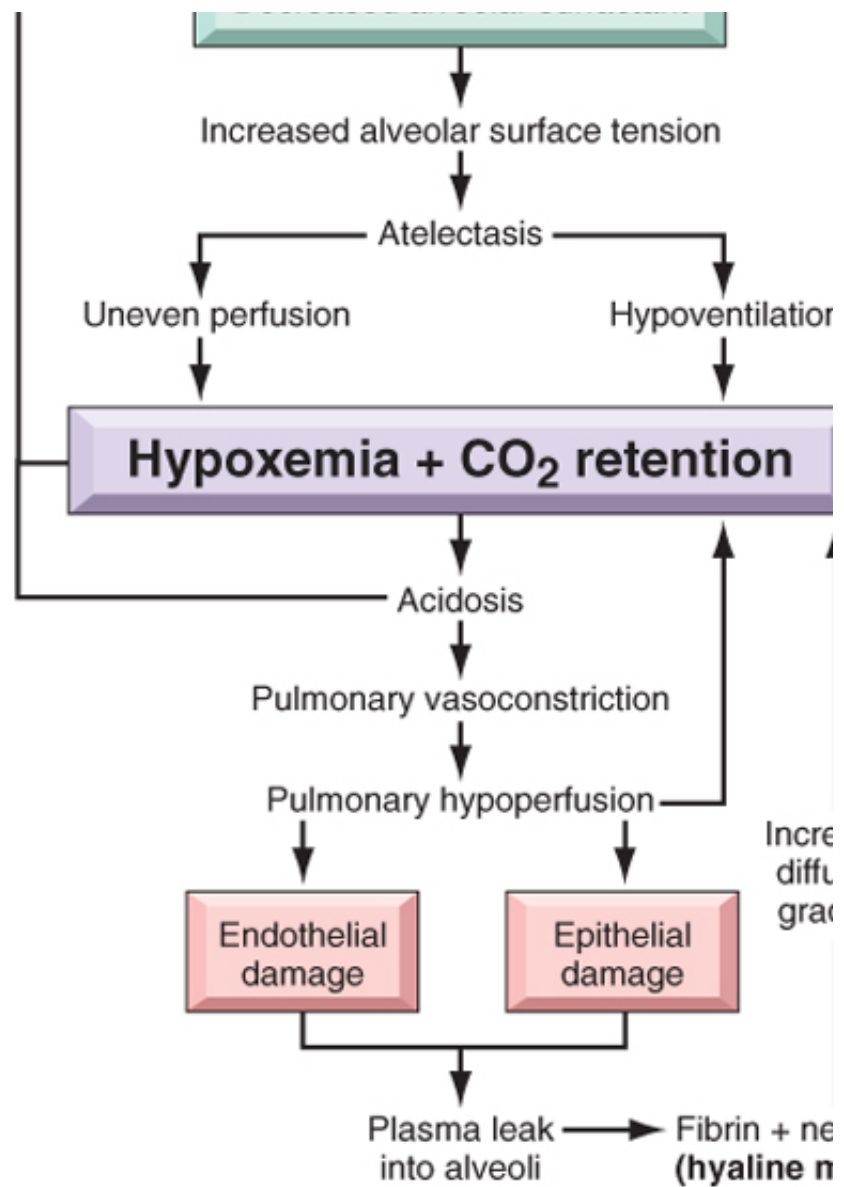
The fundamental defect in RDS is the inability of the immature lung to synthesize sufficient surface-active phospholipids, principally dipalmitoylphosphatidylcholine (lecithin), and at least two groups of proteins. Surfactant is synthesized by type II pneumocytes and, with the healthy newborn's first breath, rapidly reduces surface tension and thus decreasing the pressure required to keep alveoli open. In a lung deficient in surfactant, a relatively greater inspiratory effort is required with each breath to open the alveoli. The infant develops generalized atelectasis sets in. The resulting hypoxia sets into motion a sequence of events that lead to the formation of hyaline membranes (Fig. 7-22). As discussed later, this classic process has been greatly modified by surfactant treatment.

*Surfactant synthesis is regulated by hormones.* Corticosteroids stimulate the formation of surfactant. Therefore, conditions associated with intrauterine stress and fetal growth restriction that increase the risk of developing RDS. Surfactant synthesis can be suppressed by the compensatory high blood levels of glucose which counteracts the effects of steroids. This may explain, in part, why infants of diabetic mothers develop RDS. Labor is known to increase surfactant synthesis; hence, cesarean section before the onset of labor increases the risk of RDS.

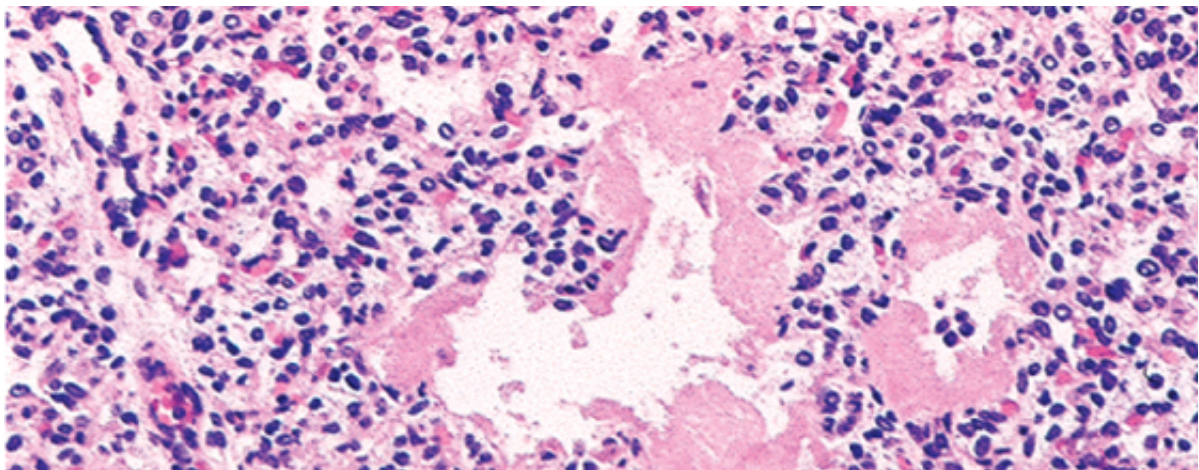
### **Morphology**

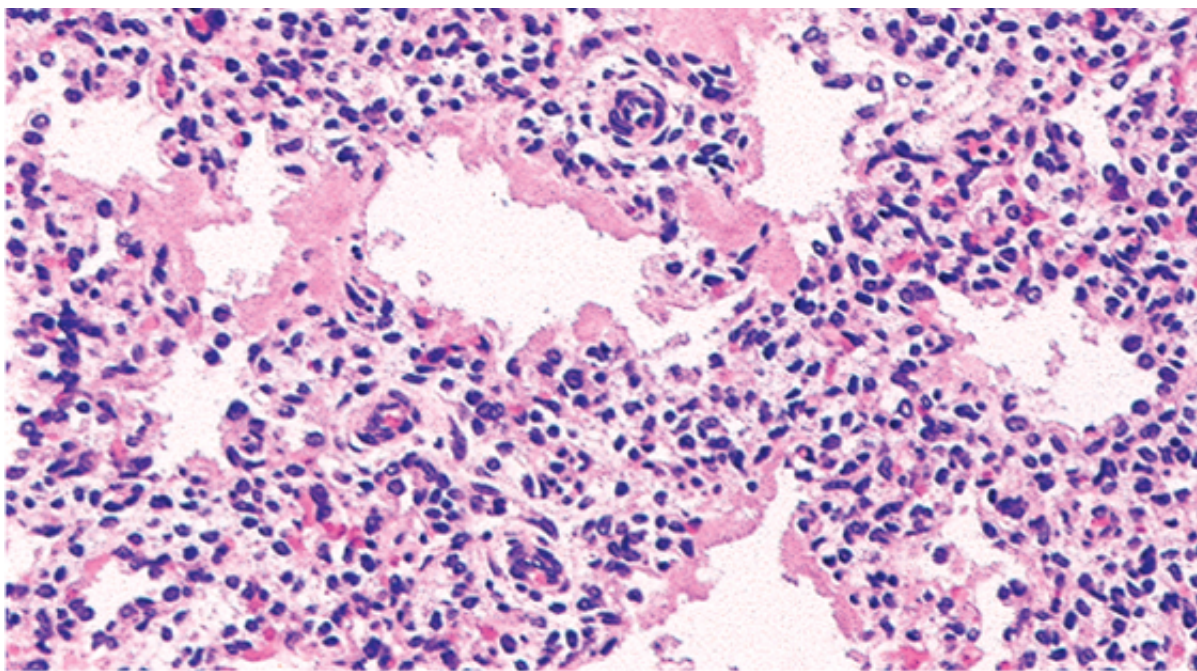
The lungs in RDS infants are of normal size but are heavy and relatively airless. They are pale pink in color, and microscopically the tissue appears solid, with poorly developed, generalized atelectasis of terminal bronchioles and alveolar ducts. Later in the course, characteristic **eosinophilic hyaline membranes** line the respiratory bronchioles, alveolar ducts, and random alveoli (Fig. 7-22). These "membranes" contain necrotic epithelial cells admixed with extravasated plasma proteins. There is a remarkable paucity of neutrophilic inflammatory reaction associated with these membranes. Hyaline membrane disease are never seen in stillborn infants or in live-born infants who die within hours of birth. If the infant dies after several days, evidence of reparative changes, such as hyperplasia of type II pneumocytes and interstitial fibrosis, is seen.





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Figure 7-22 Pathophysiology of respiratory distress syndrome (see te





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Figure 7-23 Hyaline membrane disease (H&E stain). There is alternating atelectasis and dilation of the alveoli. Note the dilated alveoli.

### Clinical Features

The classic clinical presentation before the era of treatment with exogenous surfactant was described. The course and prognosis for neonatal RDS vary, dependent on the maturity and birth weight of the infant and the timing of therapy. A major thrust in the control of RDS focuses on prevention, either by delaying labor until fetal lung maturity is achieved or by inducing maturation of the lung in the fetus at risk. Critical to these objectives is the ability to assess fetal lung maturity. Various methods have been used, including analysis of amniotic fluid phospholipids, analysis of pulmonary secretions discharged into the amniotic fluid, analysis of amniotic fluid phospholipid surfactant in the alveolar lining. Prophylactic administration of exogenous surfactant at birth to extremely premature infants (<28 weeks) has been shown to be very beneficial, such that it is now uncommon for infants to die of RDS.

In uncomplicated cases, recovery begins to occur within 3 or 4 days. In affected infants oxygen is ventilator-administered oxygen for prolonged periods is associated with two well-known complications: *retinopathy of prematurity* in the eyes, and *bronchopulmonary dysplasia (BPD)*. Fortunately, both have become less common as a result of gentler ventilation techniques, antenatal glucocorticoid therapy, and prophylactic surfactant administration.

Retinopathy of prematurity has a two-phase pathogenesis. During the *hyperoxic* phase of the disease, the pro-angiogenic vascular endothelial growth factor (VEGF) is markedly decreased, causing a decrease in retinal vascularization. When the infant is returned to relatively hypoxic room air ventilation (phase II), there is a rebound increase in VEGF, inducing retinal vascular proliferation and the characteristic lesions in the retina. The major abnormality in BPD is a decrease in the alveolar hypoxia. Thus, the current view is that BPD is most likely caused by an arrested or arrested so-called saccular stage of development. The levels of a variety of proinflammatory cytokines (including interleukin-1 and IL-8) are increased in the alveoli of infants who develop BPD, suggesting a role for inflammation in pulmonary development.

Infants who recover from RDS are also at increased risk for developing a variety of other complications. Among these are *patent ductus arteriosus*, *intraventricular hemorrhage*, and *necrotizing enterocolitis*. Advances in the management of RDS, which help save the lives of many infants with RDS, it also brings to the surface the exquisite

### SUMMARY

**Neonatal Respiratory Distress Syndrome** Neonatal RDS ("hyaline membrane disease") is a condition of prematurity (most cases occur in neonates <28 weeks gestational age). The primary abnormality in RDS is insufficient pulmonary surfactant, which results in alveolar collapse at birth. The characteristic morphology in RDS is the presence of hyaline membranes (composed of necrotic epithelial cells and plasma proteins) lining the airways. RDS can be prevented by prophylactic administration of steroids, surfactant therapy, and by improved ventilation techniques. Long-term sequelae associated with RDS therapy include retinopathy of prematurity and bronchopulmonary dysplasia; the incidence of both complications has decreased with advances in management of RDS.



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## NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) most commonly occurs in premature infants, with the incidence of the disease being inversely proportional to the gestational age. It occurs in approximately one out of 10 very-low-birth-weight infants (<1500 gm). The cause of NEC is controversial, but in all likelihood it is multifactorial. *Intestinal ischemia* is a prerequisite and may result from either generalized hypoperfusion or selective reduction of blood flow to the intestines to divert oxygen to vital organs such as the brain. Other predisposing conditions include *bacterial colonization* of the gut and administration of *formula feeds*, both of which aggravate mucosal injury in the immature bowel.

NEC typically involves the terminal ileum, cecum, and right colon, although any part of the small or large intestine may be involved. The involved segment is distended, friable, and congested (Fig. 7-24), or it can be frankly gangrenous; intestinal perforation with accompanying peritonitis may be seen. Microscopically, mucosal or transmural coagulative necrosis, ulceration, bacterial colonization, and submucosal gas bubbles are all features associated with NEC. Reparative changes, such as granulation tissue and fibrosis, may be seen shortly after the acute episode.

The clinical course is fairly typical, with the onset of bloody stools, abdominal distention, and development of circulatory collapse. Abdominal radiographs often demonstrate gas within the intestinal wall (*pneumatosis intestinalis*). When detected early NEC can be often managed conservatively, but many cases (20% to 60%) require operative intervention and resection of the necrotic segments of bowel. NEC is associated with high perinatal mortality; infants who survive often develop *post-NEC strictures* from fibrosis caused by the healing process.







## SUDDEN INFANT DEATH SYNDROME



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Figure 7-24 Necrotizing enterocolitis. **A**, Postmortem examination in a severe case shows that the entire small bowel (usually this implies impending perforation). **B**, The congested portion of the ileum corresponds to areas of hemorrhage on microscopy. Submucosal gas bubbles (*pneumatosis intestinalis*) can be seen in severe cases.

Sudden infant death syndrome (SIDS) is a disease of unknown cause. The National Institute of Child Health and Human Development defines *SIDS* as "the sudden death of an infant under 1 year of age which remains unexplained after a thorough investigation, including performance of a complete autopsy, examination of the death scene, and review of the infant's history." The most important point not stressed in the definition is that the infant usually dies while asleep, hence the pseudonyms of "cribside death" and "cot death." SIDS is the leading cause of death between 1 month and 1 year of age in this country, and the third leading cause of death in infants under 1 year of age. In 90% of cases, the infant was between the ages of 2 and 4 months.

### *Pathogenesis*

The circumstances surrounding SIDS have been explored in great detail, and it is generally accepted that there is a variable mixture of contributing causes in a given case. A "triple-risk" model of SIDS has been proposed, which involves the intersection of three overlapping variables: (1) a *vulnerable infant*, (2) a *critical developmental period*, and (3) an *exogenous stressor(s)*. According to this model, several factors make the infant vulnerable to SIDS during the critical developmental period (i.e., 1 month to 1 year). These vulnerability factors may be attributable to the infant, the exogenous stressor(s) is attributable to the environment (Table 7-10). Although numerous factors have been proposed, the most compelling hypothesis is that SIDS reflects a delayed development of the infant's autonomic nervous system.

vulnerable infant, the most compelling hypothesis is that SIDS reflects a delayed development of Regions of the brain stem, particularly the *arcuate nucleus* located in the ventral medullary surface. "arousal" response to noxious stimuli such as hypercarbia, hypoxia, and thermal stress encounter regulate breathing, heart rate, and body temperature. In certain infants, for yet inexplicable reason delay in maturation of this region, compromising the arousal response to noxious stimuli. Among the sleeping position, sleeping on soft surfaces, and thermal stress are possibly the most important risk factors. The prone position predisposes an infant to one or more recognized noxious stimuli (hypoxia, hypercarbia, and thermal stress). In addition, the prone position is also associated with decreased arousal responsiveness compared to the supine position. Studies from Europe, Australia, New Zealand, and the United States showed clearly increased risk for SIDS in the prone position, prompting the American Academy of Pediatrics to recommend placing *healthy infants on their backs* to sleep. This "Back to Sleep" campaign has resulted in substantial decreases in SIDS-related deaths.

**Table 7-10. Factors Associated with Sudden Infant Death Syndrome**

<b>Parental</b>
Young maternal age (<20 years of age)
Maternal smoking during pregnancy
Drug abuse in <i>either</i> parent, specifically paternal marijuana and maternal opiate, cocaine use
Short intergestational intervals
Late or no prenatal care
Low socioeconomic group
African American and American Indian ethnicity (? socioeconomic factors)
<b>Infant</b>
Brain stem abnormalities associated defective arousal and cardiorespiratory control
Prematurity and/or low birth weight
Male sex
Product of a multiple birth
SIDS in an earlier sibling
Antecedent respiratory infections
?Gastroesophageal reflux
<b>Environment</b>
Prone sleep position
Sleeping on a soft surface
Hyperthermia
Postnatal passive smoking
<b>Postmortem Abnormalities Detected in Cases of Sudden Unexpected Infant Death*</b>
Infections
Viral myocarditis
Bronchopneumonia
Unsuspected congenital anomaly
Congenital aortic stenosis
Anomalous origin of the left coronary artery from the pulmonary artery
Traumatic child abuse
Intentional suffocation (filicide)
Genetic and metabolic defects
Cardiac sodium and potassium ion channel mutations
Fatty acid oxidation disorders (MCAD mutations)
Cardiomyopathy secondary to mitochondrial DNA mutations

\*SIDS is not the only cause of sudden unexpected death in infancy; instead, it is a *diagnosis of exclusion*. Therefore, performance of a thorough autopsy is essential to explain the cause of sudden unexpected death. These cases should not, strictly speaking, be labeled as "SIDS."

Explain the cause of sudden unexpected death. These cases should not, strictly speaking, be labeled as SIDS. MCAD, medium-chain acyl-coenzyme A dehydrogenase.

### Morphology

Anatomic studies of victims have yielded inconsistent histologic findings. **Multiple** common finding in the typical SIDS autopsy (~80% of cases); these are usually pre visceral and parietal pleura, and epicardium. Grossly, the lungs are usually congested with or without **pulmonary edema** is demonstrable microscopically. Sophisticated morphometric studies have revealed quantitative brain stem abnormalities **of the arcuate nucleus** or a subtle decrease in brain stem neuronal populations in observations are not uniform, however, and not amenable to most "routine" autopsies.

It should be noted that SIDS is not the only cause of sudden unexpected deaths in diagnosis of exclusion, requiring careful examination of the death scene and a careful examination. The latter can reveal an unsuspected cause of sudden death in as many as 10% of "SIDS" babies (see Table 7-10). Infections (e.g., viral myocarditis or bronchopneumonia) are common causes of sudden "unexpected" death, followed by an unsuspected congenital or acquired cardiac disease. With the advent of advancements in molecular diagnostics, several genetic causes of sudden "unexpected" death have emerged. For example, fatty acid oxidation disorders, characterized by defects in respiratory chain oxidative enzymes, may be responsible for as many as 5% of sudden deaths in infants. Deficiency in medium-chain acyl-coenzyme A dehydrogenase is the most common of these. Mutations of cardiac sodium and potassium channels have also been identified. Some forms of cardiac arrhythmia characterized by prolonged QT intervals; these account for a small percentage of SIDS deaths. SIDS in an earlier sibling is associated with a fivefold relative risk of recurrence. Child abuse must be carefully excluded under these circumstances.

### SUMMARY

**Sudden Infant Death Syndrome** SIDS is a disease of *unknown cause*, defined as the sudden death of an infant younger than 1 year of age, which remains unexplained after a thorough investigation including performance of an autopsy. Most cases occur between 1 and 18 months of age. The most likely basis for SIDS is a delayed development in arousal and respiratory control. Numerous risk factors have been proposed, of which the prone sleep position is the most widely recognized; hence the success of the "Back to Sleep" program in reducing the incidence of SIDS.





## FETAL HYDROPS

Fetal hydrops refers to the accumulation of edema fluid in the fetus during intrauterine growth. The most important are listed in [Table 7-11](#). Until recently, hemolytic anemia caused by Rh blood group incompatibility between mother and fetus (immune hydrops) was the most common cause, but with the successful prophylaxis of this condition, nonimmune hydrops have emerged as the principal culprits. Notably, the intrauterine fluid accumulation is usually progressive, generalized edema of the fetus (*hydrops fetalis*), a usually lethal condition, to more localized isolated pleural and peritoneal effusions, or postnuchal fluid accumulation (*cystic hygroma*) that are usually not fatal. The mechanism of immune hydrops will be discussed first, followed by other important causes of nonimmune hydrops.

**Table 7-11. Major Causes of Fetal Hydrops\***

<b>Cardiovascular</b>
Malformations
Tachyarrhythmia
High-output failure
<b>Chromosomal</b>
Turner syndrome
Trisomy 21, Trisomy 18
<b>Fetal Anemia</b>
Homozygous $\alpha$ -thalassemia
Parvovirus B19
Immune hydrops (Rh and ABO incompatibility)
<b>Twin Gestation</b>
Twin-twin transfusion
<b>Infection</b> (excluding parvovirus)
Cytomegalovirus
Syphilis
Toxoplasmosis
<b>Major Malformations</b>
<b>Tumors</b>
<b>Metabolic Disorders</b>

\*The cause of fetal hydrops may be undetermined ("idiopathic") in as many as 20% of cases.

Modified from Machin GA: Hydrops, cystic hygroma, hydrothorax, pericardial effusions, and fetal ascites. In Gilbert-Barnes (ed): Pediatric Pathology. Mosby, 1997.

### Immune Hydrops

Immune hydrops results from an antibody-induced *hemolytic disease in the newborn* that is caused by incompatibility between mother and fetus. Such an incompatibility occurs only when the fetus inherits red cell antigenic determinants from the mother. The most common antigens to result in clinically significant hemolysis are the Rh antigens. Although numerous antigens included in the Rh system, only the D antigen is a major cause of Rh incompatibility. The mother is sensitized during maternal circulation during the last trimester of pregnancy, when the cytotrophoblast is no longer intact (fetomaternal bleed). The mother thus becomes sensitized to the foreign antigen and develops antibodies that cross the placenta to the fetus and cause red cell destruction. Once immune hemolysis is initiated, there is resultant tissue ischemia, intrauterine cardiac failure, and peripheral pooling of fluid (edema). As a result, the final pathway by which edema occurs in many cases of nonimmune hydrops as well.

Several factors influence the immune response to Rh-positive fetal red cells that reach the maternal circulation.



Concurrent ABO incompatibility protects the mother against Rh immunization, because the iso-hemagglutinins are removed from the maternal circulation. The antibody response depends on the presence of fetal red cells in the maternal circulation. Hence, hemolytic disease develops only when the mother has experienced a significant transfusion of fetal red cells. The isotype of the antibody is important, because immunoglobulin G (IgG) (but not IgM) can cross the placenta. The initial exposure to Rh antigen evokes the formation of IgM antibodies, so Rh disease is a second pregnancy problem. Subsequent exposure during the second or third pregnancy generally leads to



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 Figure 7-25 Hydrops fetalis. **A**, Generalized accumulation of fluid in the fetus. **B**, Fluid accumulation particularly in the neck region, a condition has been termed *cystic hygroma*. Cystic hygromas are characteristically seen with, but not limited to, chromosomal abnormalities. (Courtesy of Dr. Beverly Rogers, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas)

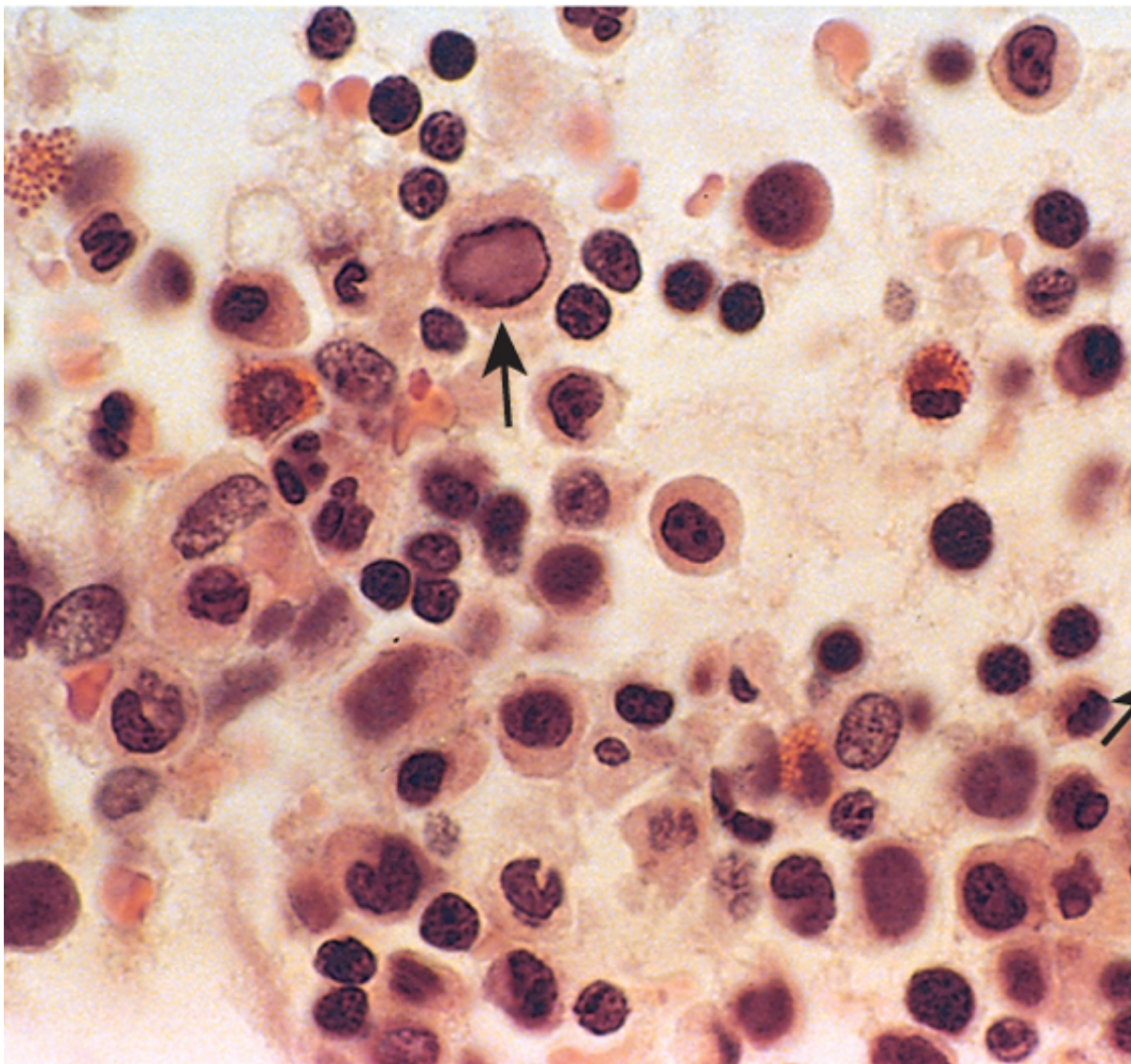
Appreciation of the role of prior sensitization in the pathogenesis of Rh-hemolytic disease of the newborn. Currently, Rh-negative mothers are given anti-D globulin soon after the delivery of an Rh-positive infant to prevent sensitization. Antigenic sites on the fetal red cells that may have leaked into the maternal circulation during childbirth are destroyed by the anti-D globulin.



sensitization to Rh antigens.

As a result of the remarkable success achieved in prevention of Rh hemolysis, fetomaternal ABO incompatibility has become a common cause of immune hemolytic disease of the newborn. Although ABO incompatibility occurs in many pregnancies, only a small fraction of infants subsequently born develop hemolysis, and in general the disease is mild. ABO hemolytic disease occurs almost exclusively in infants of group A or B whose mothers are of group O. Anti-A and anti-B isohemagglutinins in group O mothers are usually of the IgM type and so do not cross the placenta. However, certain group O women possess IgG antibodies directed against group A or B antigens, and these can cross the placenta and sensitize the fetus. Therefore, the firstborn may be affected. Fortunately, even with transplacental sensitization, the incidence of hemolytic disease resulting from ABO incompatibility is minimal. There is no effective method of preventing hemolytic disease resulting from ABO incompatibility.

### Nonimmune Hydrops



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Figure 7-26 Bone marrow from an infant infected with parvovirus B19. The arrows point to two erythroid precursors and a surrounding peripheral rim of residual chromatin.

The major causes of nonimmune hydrops include those associated with *cardiovascular defects*, *c*  
Both structural cardiovascular defects and functional abnormalities (i.e., arrhythmias) may result in

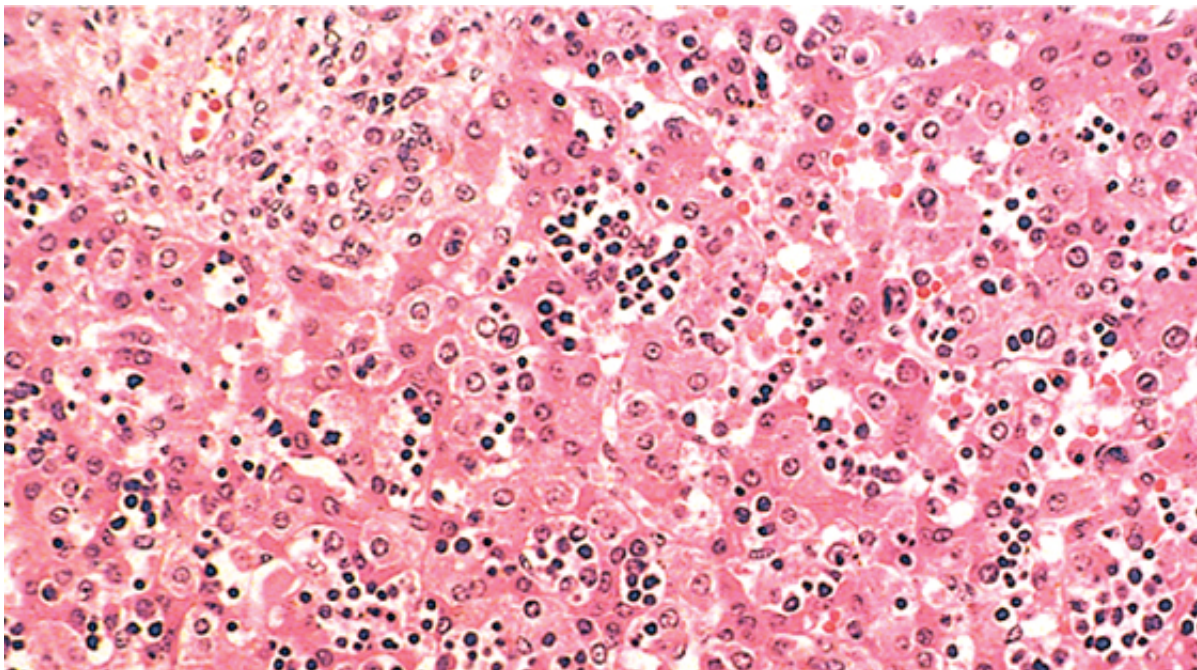
Among the chromosomal anomalies, 45,X karyotype (Turner syndrome) and trisomies 21 and 18 are the basis for this is the presence of underlying structural cardiac anomalies, although in Turner syndrome lymphatic drainage from the neck leading to postnuchal fluid accumulation (*cystic hygromas*). Fetal or ABO incompatibility also result in hydrops. In fact, in some parts of the world (e.g., Southeast Asia) homozygous  $\alpha$ -thalassemia is probably the most common cause of fetal hydrops. Transplacental infection is increasingly recognized as an important cause of fetal hydrops. The virus gains entry into erythrocytes and replicates. This leads to erythrocyte maturation arrest and aplastic anemia. Parvoviral intranuclear inclusions are seen in fetal and marrow erythroid precursors (Fig. 7-26). The basis for fetal hydrops in fetal anemia is fetal anemia with secondary myocardial dysfunction and circulatory failure. Additionally, secondary liver dysfunction contributing to hypoalbuminemia, reduced plasma osmotic pressure, and edema.

### Morphology

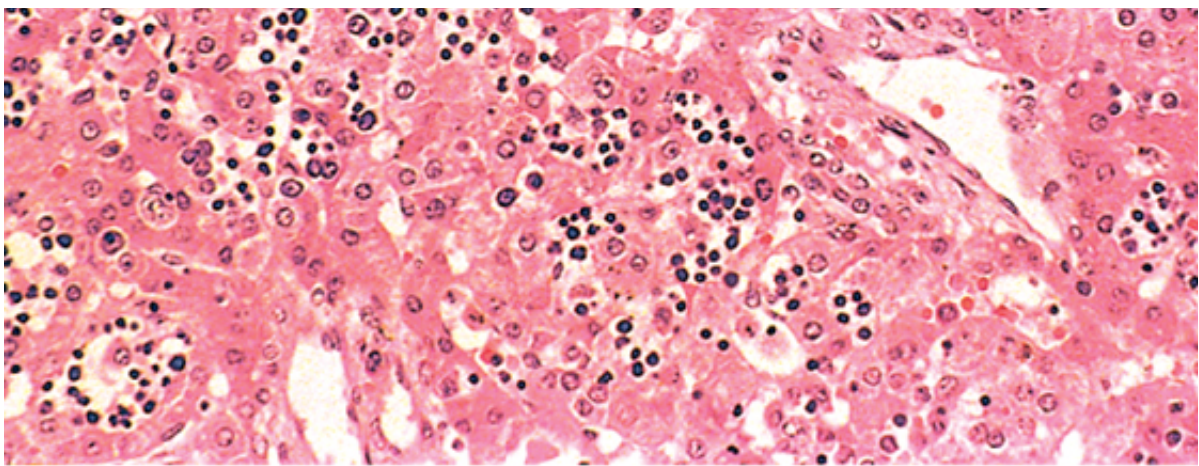
The anatomic findings in fetuses with intrauterine fluid accumulation vary with both the degree and the underlying etiology. As previously noted, **hydrops fetalis** represents the most generalized manifestation (see Fig. 7-25), and lesser degrees of edema such as isolated skin edema or postnuchal fluid collections can occur. Accordingly, infants may be stillborn, die shortly after birth, or recover completely. The presence of dysmorphic features suggests underlying congenital abnormalities; postmortem examination may reveal a cardiac anomaly. In hydrops due to anemia, both fetus and placenta are characteristically pale; in most cases, the liver is enlarged due to **cardiac failure** and congestion. Additionally, the bone marrow shows compensatory erythroid precursors (parvovirus-associated aplastic anemia being a notable exception). **Hematopoiesis** is present in the liver, the spleen, and possibly other tissues such as the lungs and even the heart. The increased hematopoietic activity accounts for the presence in the circulation of large numbers of immature red cells, including reticulocytes, normoblasts, and even myeloid cells (**erythroblastosis fetalis**) (Fig. 7-27).

The presence of hemolysis in Rh or ABO incompatibility is associated with the addition of increased circulating bilirubin from the red cell breakdown. The CNS may be damaged. Hyperbilirubinemia is marked (usually above 20 mg/dL in full-term infants, often less in premature infants). The circulating unconjugated bilirubin is taken up by the brain tissue, on which it has a toxic effect. The basal ganglia and brain stem are particularly prone to deposition of bilirubin, which imparts a characteristic yellow hue to the parenchyma (**kernicterus**; Fig. 7-28).

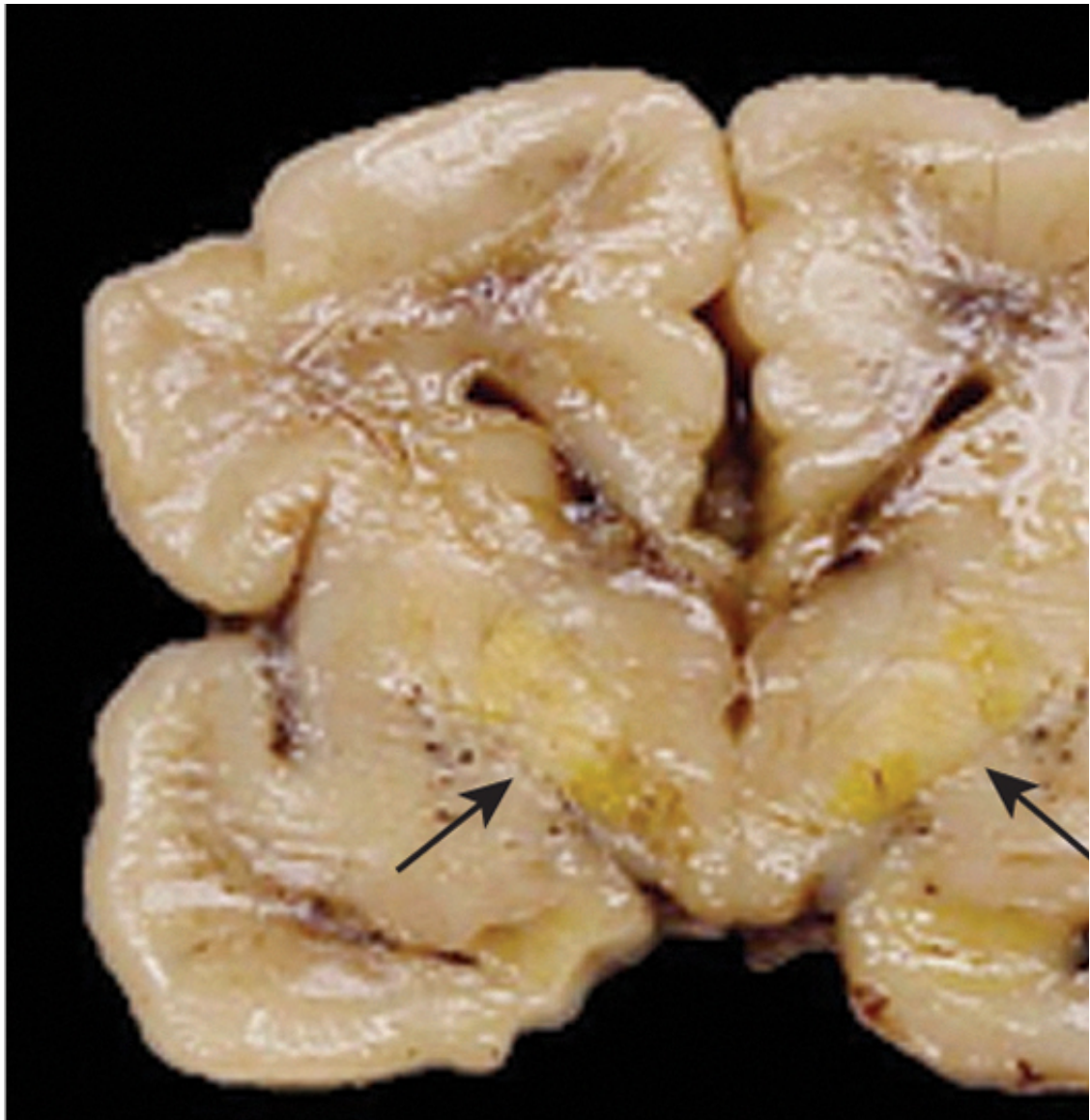
### Clinical Course







© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentc  
 Figure 7-27 Numerous islands of extramedullary hematopoiesis (small *blue* cells) are scattered among mature he  
 fetalis.





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 Figure 7-28 Kernicterus. Severe hyperbilirubinemia in the neonatal period—for example, secondary to immune hemolytic disease (arrows) in the brain parenchyma. This occurs because the blood-brain barrier is less well developed in the neonate and can survive develop long-term neurologic sequelae.

Early recognition of intrauterine fluid accumulation is imperative, since even severe cases can survive with available therapy. Fetal hydrops that results from Rh incompatibility may be more or less accurately predicted with rapidly rising Rh antibody titers in the mother during pregnancy. Amniotic fluid obtained by amniocentesis contains bilirubin. The human antiglobulin test (Coombs test, [Chapter 12](#)) is positive on fetal cord blood if there is no maternal antibody. Antenatal exchange transfusion is an effective form of therapy. Postnatally, phototherapy converts bilirubin to readily excreted dipyrroles. As already discussed, in an overwhelming majority of cases, maternal antibodies to the mother can prevent the occurrence of immune hydrops in subsequent pregnancies. Fetal hydrops is difficult to predict but is readily anticipated by awareness of the blood incompatibility between mother and fetus. Bilirubin determinations in the vulnerable newborn infant. Needless to say, in fatal instances of fetal hydrops, examination is imperative to determine the cause and to exclude a potentially recurring cause such as Rh incompatibility.

## SUMMARY

**Fetal Hydrops** Fetal hydrops refers to the accumulation of edema fluid in the fetus. The degree of fluid accumulation is variable, from generalized hydrops to localized cystic hygromas. The most common causes of fetal hydrops are *nonimmune* hydrops (chromosomal abnormalities, cardiovascular defects, and fetal anemia), while immune hydrops is frequent due to Rh antibody prophylaxis. Erythroblastosis fetalis (circulating red blood cell precursors) is a characteristic finding of fetal anemia-associated hydrops. Hemolytic hyperbilirubinemia can result in kernicterus in the basal ganglia and brain stem of premature infants.





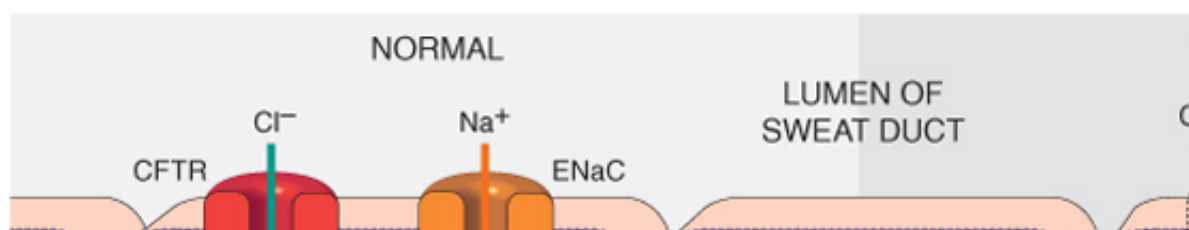
## CYSTIC FIBROSIS

With an incidence of 1 in 3200 live births in the United States, *cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasian populations*. It is uncommon among Asians (1 in 31,000 live births) and African Americans. CF is inherited by simple *autosomal recessive* transmission, and does not affect heterozygote carriers. There is, however, significant phenotypic variation that results from diverse mutations in the CF-associated gene, the tissue-specific expression of the gene, and the influence of newly recognized disease modifiers. It is fundamentally a *widespread disorder characterized by abnormal secretion in exocrine glands and the epithelial lining of the respiratory, gastrointestinal (GI), and reproductive tracts*. The thick, viscid mucus secretions that block the airways and the pancreatic ducts are responsible for the two most recurrent and chronic complications: recurrent pulmonary infections and pancreatic insufficiency. In addition, although the sweat glands are normal (and remain so throughout the course of this disease), a *high level of sodium chloride<sub>Rx</sub> in sweat is a characteristic biochemical abnormality in CF*.

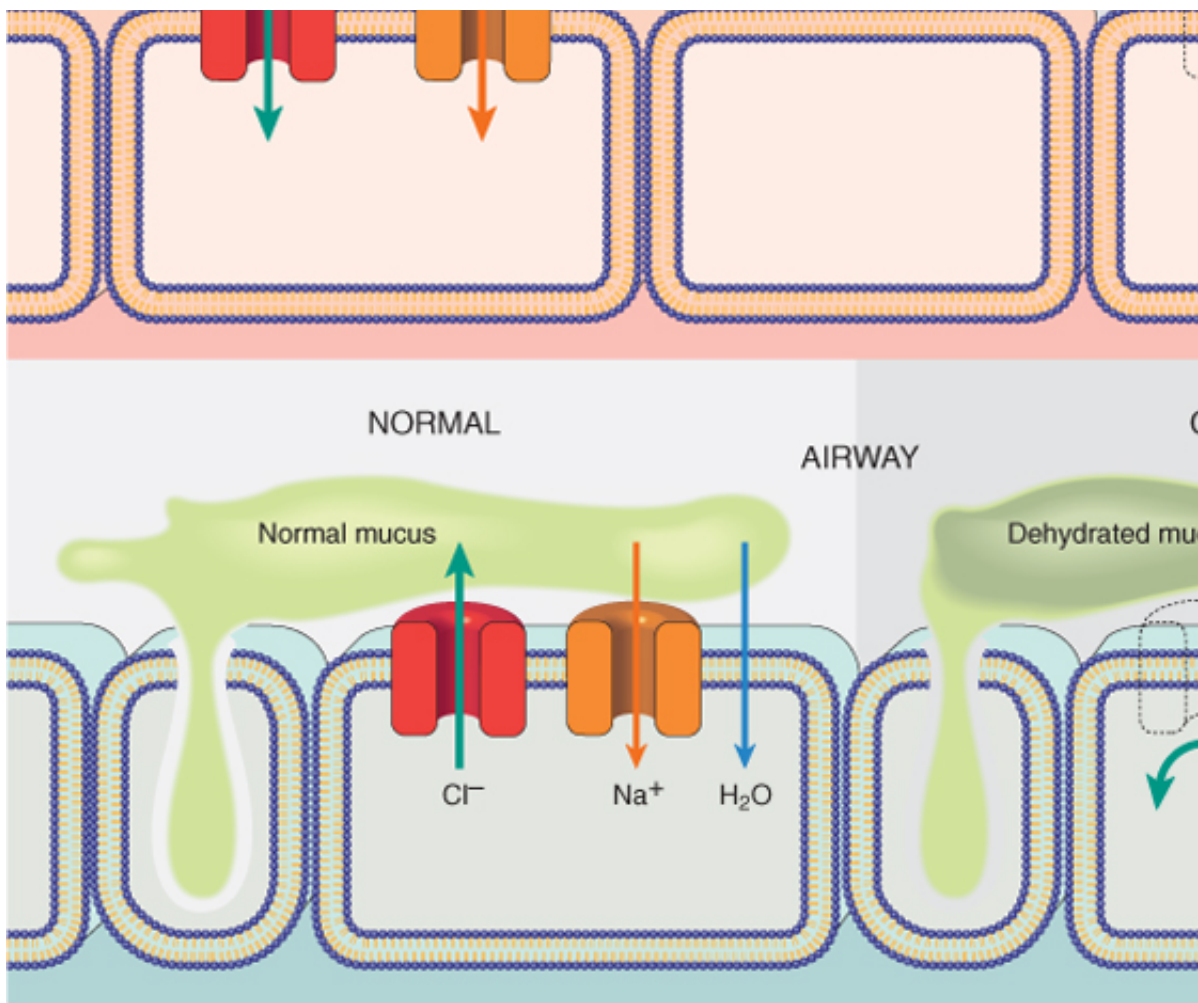
### Pathogenesis

The primary defect in CF is abnormal function of an epithelial chloride channel protein encoded by the *CFTR* gene on chromosome 7q31.2. The changes in mucus are considered secondary to the defect in chloride ion transport. In normal epithelia the transport of chloride ions across the cell membrane occurs through *CFTR* that form chloride channels. Mutations in the *CFTR* gene render the epithelial membranes impermeable to chloride ions (Fig. 7-29). However, the impact of this defect on transport function is tissue-specific. The major function of the sweat gland ducts is to reabsorb luminal chloride ions and augment sodium reabsorption. Therefore, in the sweat ducts, the defect leads to decreased reabsorption of *sodium chloride<sub>Rx</sub>* and production of hypertonic sweat (see Fig. 7-29). In the exocrine glands, *CFTR* in the respiratory and intestinal epithelium forms one of the most important avenues for chloride secretion. At these sites, *CFTR* mutations result in loss or reduction of chloride secretion into the lumen (see Fig. 7-29). Since sodium absorption is also increased, and both of these ion changes increase passive water reabsorption, the water content of the surface fluid layer coating mucosal cells is decreased. Thus, unlike the sweat ducts, there is dehydration of the surface fluid layer coating the respiratory and intestinal mucosal cells in normal versus individuals with CF. This dehydration of the surface fluid layer in the respiratory and intestinal complications in CF seems to stem from an isotonic but low-volume secretions. This dehydration leads to defective mucociliary action and the accumulation of concentrated, viscid secretions that predispose to recurrent pulmonary infections.

Since the *CFTR* gene was cloned in 1989, more than 800 disease-causing mutations have been identified. Mutations are classified as "severe" or "mild" depending on the location of the mutation in the gene sequence; "severe" mutations result in a complete loss of *CFTR* protein function, while the product of a "mild" mutation retains residual function. The most common mutation is a deletion of 3 nucleotides coding for phenylalanine at amino acid position 508 ( $\Delta F508$ ). This is an autosomal recessive disease. Worldwide,  $\Delta F508$  mutation can be found in approximately 70% of CF patients. Since CF is an autosomal recessive disease, individuals harbor mutations on both alleles. As discussed later, the combination of mutations on both alleles determines the phenotype, as well as organ-specific manifestations. Although CF remains one of the best known examples of a single gene defect, there is increasing evidence that *genetic modifiers* besides *CFTR* modulate the frequency and severity of the manifestations. One example of a candidate genetic modifier is *mannose-binding lectin*, a key effector in the opsonization and phagocytosis of microorganisms. Polymorphisms in one or both mannose-binding lectin alleles that affect the function of the protein are associated with a threefold higher risk of end-stage lung disease, and reduced survival in the setting of CF.







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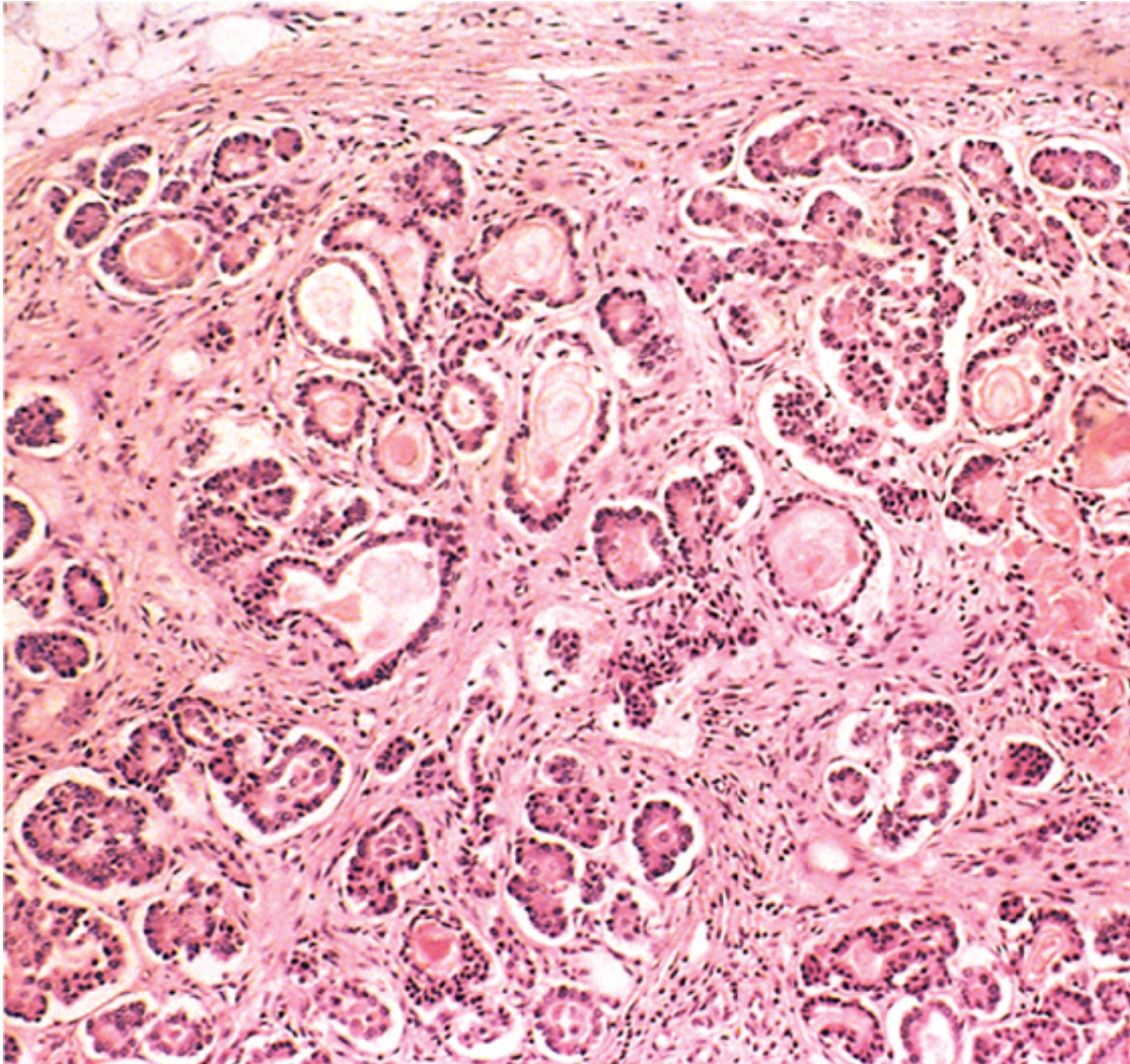
Figure 7-29 Chloride channel defect in the sweat duct (top) causes increased chloride and sodium concentration in the sweat. This leads to decreased chloride secretion and increased sodium and water reabsorption leading to dehydration of the mucous lining, mucus plugging of airways, and mucus plugging of airways. CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel.

### Morphology

The anatomic changes are highly variable and depend on which glands are affected in this involvement. **Pancreatic abnormalities** are present in 85% to 90% of patients. In mild cases, there may be only accumulations of mucus in the small ducts with some dilatation of the glands. In more advanced cases, usually seen in older children or adolescents, the disease causes atrophy of the exocrine glands and progressive fibrosis (Fig. 7-30). The total exocrine secretion impairs fat absorption, and so avitaminosis A may contribute to the lining epithelium of the ducts in the pancreas, which are already injured by the secretions. Thick viscid plugs of mucus may also be found in the small intestine of patients with cystic fibrosis, known as **meconium ileus**.

The **pulmonary changes** are the most serious complications of this disease (Fig. 7-31). The viscous mucus secretions of the submucosal glands of the respiratory tree with chronic infection and inflammation of the air passages. The bronchioles are often distended with thick mucus. There is marked hyperplasia and hypertrophy of the mucus-secreting cells. Superimposed on this is severe chronic bronchitis and bronchiectasis. In many instances, lung abscesses caused by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are the three most common organisms responsible for lung infections. Even more sinister is the increasing frequency of infection with the opportunistic bacterium *Burkholderia cepacia*. This opportunistic bacterium is particularly harmful in patients with cystic fibrosis.

organism has been associated with fulminant illness. The **liver involvement** follows. Bile canaliculi are plugged by mucinous material, accompanied by ductular proliferation and inflammation. Hepatic **steatosis** is a common finding in liver biopsies. Over time, cirrhosis can develop, resulting in diffuse hepatic nodularity. Such severe hepatic involvement is encountered in 5% of patients. **Azoospermia and infertility** are found in 95% of the males who survive. **Bilateral absence of the vas deferens** is a frequent finding in these patients. In some cases, this is the only feature suggesting an underlying *CFTR* mutation.



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Figure 7-30 Mild to moderate CF changes in the pancreas. The ducts are dilated and plugged with eosinophilic mucin, and the surrounding tissue is replaced by fibrous tissue.

### *Clinical Course*

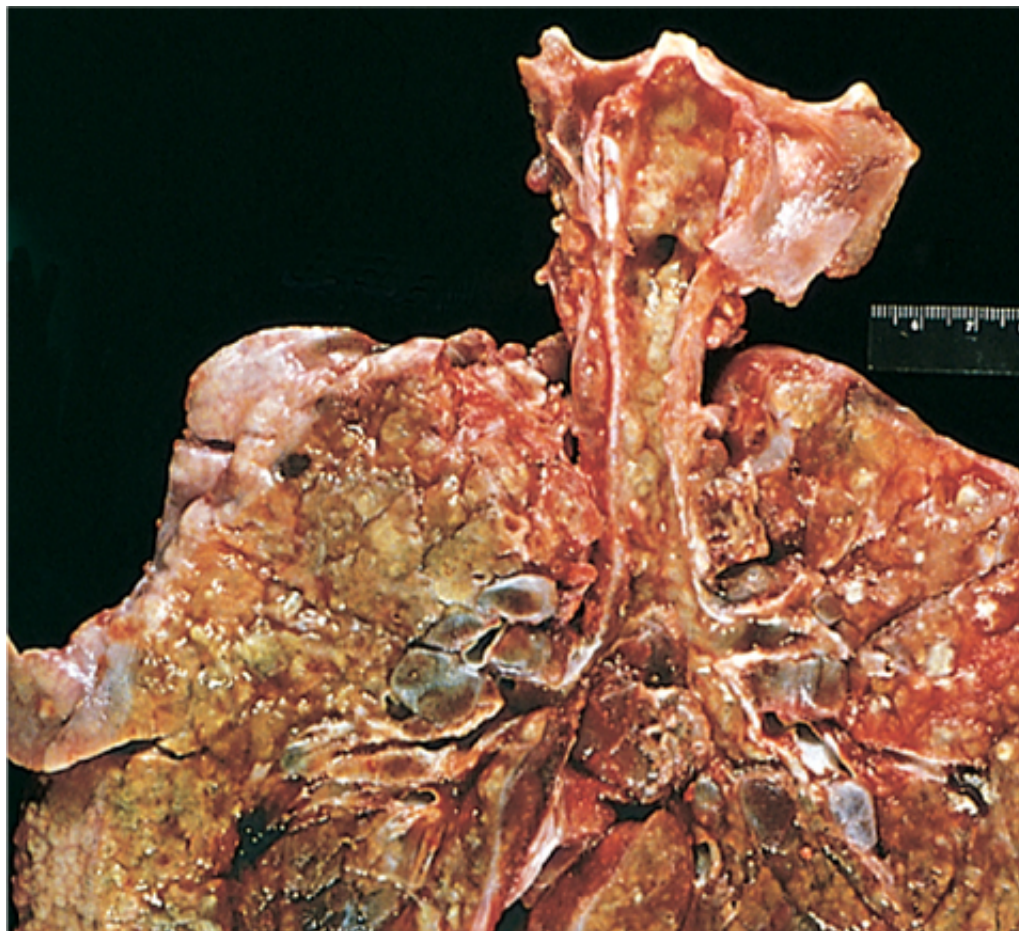
Few childhood diseases are as protean as CF in clinical manifestations. The symptoms are extremely severe, from onset at birth to onset years later, and from involvement of one organ system to involvement of many. In 10% of the cases come to clinical attention at birth or soon after because of an attack of *meconium* ileus. This occurs in the majority (85% to 90%) of patients with CF and is associated with "severe" *CFTR* mutations.

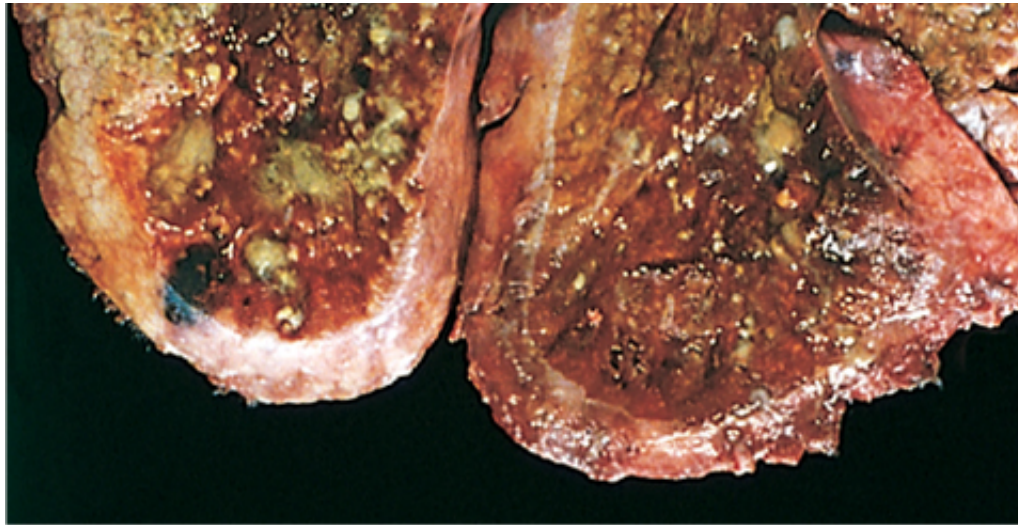


$\Delta F508$ ), whereas 10% to 15% of patients with one "severe" and one "mild" *CFTR* mutation, or two pancreatic exocrine function so as not to require enzyme supplementation (*pancreas-sufficient* phenotype associated with malabsorption of protein and fat and increased fecal loss. Manifestations of malabsorption (steatorrhea, abdominal distention; and poor weight gain) appear during the first year of life. The faulty fat absorption of fat-soluble vitamins, resulting in manifestations of avitaminosis A, D, or K. Hypoproteinemia may lead to edema. Persistent diarrhea may result in rectal prolapse in as many as 10% of children with CF. This is usually not associated with other GI complications, and in general, these individuals demonstrate no pancreatic insufficiency. "Idiopathic" chronic pancreatitis occurs in a subset of patients with pancreas-sufficient CF and is associated with life-threatening complications.

Cardiorespiratory complications, such as chronic cough, persistent lung infections, obstructive pulmonary disease, are the most common cause of death (~80%) in patients followed by most CF centers in the United States. The majority of patients with classic CF harbor *P. aeruginosa*, and 3.5% harbor *B. cepacia*. With the indiscriminate use of antibiotics, there has been an unfortunate resurgence of resistant strains of *Pseudomonas* in patients with CF. Nasal polyps can occur in as many as 10% to 25% of patients with CF, and hence, children who present with nasal polyps should be evaluated for abnormalities of sweat chloride. Significant liver disease occurs late in the natural history of CF as a result of pulmonary and pancreatic involvement; however, with increasing life expectancies, liver disease has become a major cause of death. In fact, next to cardiopulmonary and transplantation-related complications, liver disease is the third most common cause of death in CF patients.

In most cases, the diagnosis of CF is based on persistently elevated sweat electrolyte concentrations (measured by the sweat chloride test), characteristic clinical findings (sinopulmonary disease, recurrent respiratory infections, and growth retardation), and family history. Sequencing the *CFTR* gene is of course the "gold standard" for the diagnosis of CF. Testing for carrier status in family members (or both) suggesting this diagnosis, genetic analysis may be warranted. Advances in the management of CF are now allowing more patients to survive into adulthood; the median life expectancy approaches 30 years and is increasing. With gene therapy in humans are still in their early stages but provide a source of encouragement for the future.





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 Figure 7-31 Lungs of a patient dying of CF. There is extensive mucous plugging and dilation of the tracheobronchial tree, which is consolidated by a combination of both secretions and pneumonia-the green color associated with *Pseudomonas* infection. (From Kumar et al, Robbins Basic Pathology, 8e, Philadelphia, PA: Elsevier, 2008, pp 101-102.)

## SUMMARY

**Cystic Fibrosis** CF is an autosomal recessive disease caused by mutations encoding the CF transmembrane regulator. The principal defect is of chloride channels, leading to high salt concentrations in sweat, and viscous luminal secretions in respiratory tract. Mutations can be severe ( $\Delta F508$ ), resulting in multisystem disease, or mild and severity. Cardiopulmonary manifestations are the most common cause of death. Chronic infections, especially with resistant pseudomonads, are frequent. Bronchiectasis and failure are long-term sequelae. Pancreatic insufficiency is extremely common; congenital bilateral absence of vas deferens is a characteristic finding in adult males.



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## TUMORS AND TUMOR-LIKE LESIONS OF INFANCY AND CHILDHOOD

Malignant neoplasms are the second most common cause of death in children between the ages higher toll. Benign tumors are even more common than are cancers.

It is difficult to segregate, on morphologic grounds, true tumors from tumor-like lesions in the infar categories of tumor-like lesions should be recognized.

*Heterotopia* or *choristoma* refers to microscopically normal cells or tissues that are present in abn pancreatic tissue "rest" found in the wall of the stomach or small intestine, or a small mass of adre ovaries, or elsewhere. Heterotopic rests are usually of little significance, but they can be confused

*Hamartoma* refers to an excessive but focal overgrowth of cells and tissues native to the organ in elements are mature and identical to those found in the remainder of the organ, they do not repro surrounding tissue. Hamartomas can be thought of as the linkage between malformations and nei between a hamartoma and a benign neoplasm is frequently tenuous and is variously interpreted. I rhabdomyomas of the heart, and adenomas of the liver are considered by some to be hamartoma

### Benign Tumors

Virtually any tumor may be encountered in the pediatric age group, but three-hemangiomas, lymph teratomas-deserve special mention here because they occur commonly in childhood.

*Hemangiomas* are the most common tumors of infancy. Both cavernous and capillary hemangioma although the latter are often more cellular than in adults, and hence are deceptively worrisome. In in the skin, particularly on the face and scalp, where they produce flat to elevated, irregular, red-bl referred to as *port wine stains*. Hemangiomas may enlarge as the child gets older, but in many ins 7-32). The vast majority of superficial hemangiomas have no more than a cosmetic significance; r hereditary disorder associated with disease within internal organs, such as the von Hippel-Lindau 23).







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 Figure 7-32 Congenital capillary hemangioma at birth (A) and at 2 years of age (B) after the lesion had underg  
 Eduardo Yunis, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylv

*Lymphangiomas* represent the lymphatic counterpart of hemangiomas. They are characterized by endothelial cells and surrounded by lymphoid aggregates; the spaces usually contain pale fluid. T importantly, are also encountered in the deeper regions of the neck, axilla, mediastinum, and retro benign, they tend to increase in size after birth and may encroach on mediastinal structures or ne

*Sacroccygeal teratomas* are the most common germ cell tumors of childhood, accounting for 40 of the overlap in the mechanisms underlying teratogenesis and oncogenesis, it is interesting that ; teratomas are associated with congenital anomalies, primarily defects of the hindgut and cloacal r meningocele, spina bifida) not believed to result from local effects of the tumor. Approximately 75% mature with a benign course, and about 12% are unmistakably malignant and lethal ([Chapter 18](#)). teratomas, and their malignant potential correlates with the amount of immature tissue elements p encountered in younger infants (<4 months), whereas children with malignant lesions tend to be s

### **Malignant Tumors**

The organ systems involved most commonly by malignant neoplasms in infancy and childhood in tissue, and soft tissues ([Table 7-12](#)). This is in sharp contrast to adults, in whom tumors of the lun common forms. Malignant tumors of infancy and childhood differ biologically and histologically fro are as follows:

Relatively frequent demonstration of a close relationship between abnormal development ( (oncogenesis)Prevalence of constitutional genetic abnormalities or syndromes that predis neonatal malignancies to spontaneously regress or undergo "differentiation" into mature el childhood tumors, so that more attention is now being paid to minimizing the adverse delay radiotherapy in survivors, including the development of second malignancies



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Figure 7-33 Sacroccocygeal teratoma. Note the size of the lesion compared with t

**Table 7-12. Common Malignant Neoplasms of Infancy and Childhood**

<b>0-4 Age yr</b>	<b>5-9 Age yr</b>
Leukemia	Leukemia
Retinoblastoma	Retinoblastoma
Neuroblastoma	Neuroblastoma

Wilms' tumor	Hepatocellular carcinoma
Hepatoblastoma	Soft tissue sarcoma
Soft tissue sarcoma (especially rhabdomyosarcoma)	CNS tumors Ewing tumor
Teratomas	Lymphoma
CNS tumors	

CNS, central nervous system.

Histologically, many malignant pediatric neoplasms are unique. In general, they tend to have a primitive, pleomorphic-anaplastic microscopic appearance, and frequently they exhibit features of organogenesis. Because of their primitive histologic appearance, many childhood tumors have been collectively referred to as *primitive tumors*. These are characterized by sheets of cells with small, round nuclei. The tumors in this category include rhabdomyosarcoma, Ewing sarcoma (peripheral neuroectodermal tumor), and some cases of Wilms' tumor. The distinctive features to render a definitive diagnosis on the basis of histologic examination alone, but radiographic findings, combined with ancillary studies (e.g., chromosome analysis, immunoperoxidase staining) are used. Three common tumors—neuroblastoma, retinoblastoma, and Wilms' tumor—are described here as pediatric tumors and those in adults.

### Neuroblastoma

The term "neuroblastic tumor" includes tumors of the sympathetic ganglia and adrenal medulla that arise from the cells populating these sites; neuroblastoma is the most important member of this family. It is the second most common childhood cancer after brain tumors, accounting for 7% to 10% of all pediatric neoplasms, and as many as 15% in infancy. Neuroblastomas demonstrate several unique features in their natural history, including spontaneous regression or *therapy-induced maturation*. Most occur sporadically, but a few are familial with autosomal dominant inheritance. Some neoplasms may involve both of the adrenals or multiple primary autonomic sites.

#### Morphology

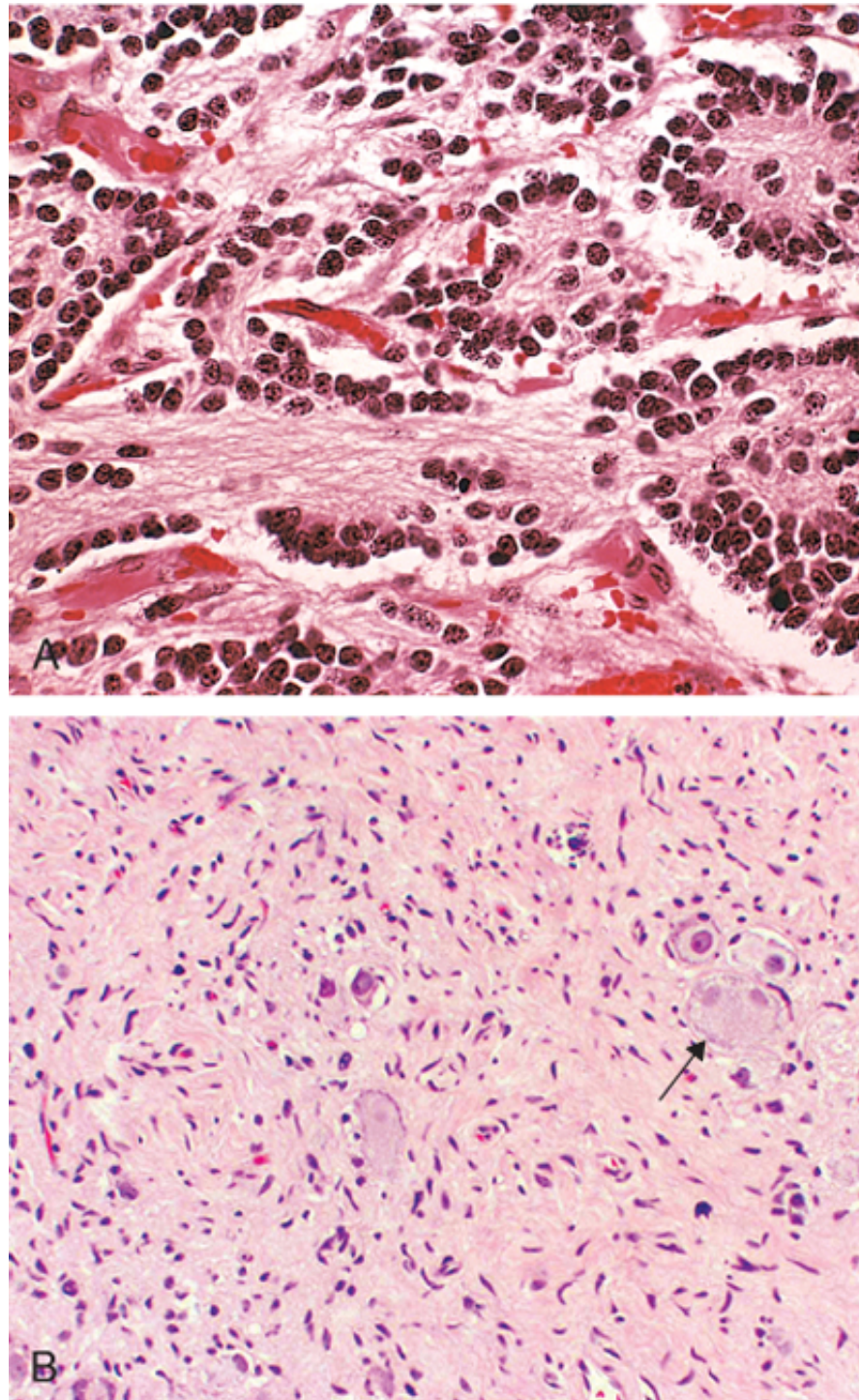
In childhood, about 40% of neuroblastomas arise in the **adrenal medulla**. The remainder arise along the sympathetic chain, with the most common locations being the paravertebral region (25%) and posterior mediastinum (15%). Macroscopically, neuroblastomas range in size from small (the in situ lesions) to large masses weighing more than 1 kg. In situ neuroblastomas are much more frequent than overt tumors. The great preponderance of these silent lesions is due to their tendency to regress, leaving only a focus of fibrosis or calcification in the adult. Some neuroblastomas are circumscribed with a fibrous pseudo-capsule, but others are far more infiltrative and invade adjacent structures, including the kidneys, renal vein, and vena cava, and envelop the aorta. The tumor is composed of soft, gray-tan, brainlike tissue. Larger tumors have areas of necrosis and hemorrhage.

Histologically, classic neuroblastomas are composed of small, primitive-appearing cells with scant cytoplasm, and poorly defined cell borders growing in solid sheets (Fig. 7-34). The cells show nuclear breakdown ("karyorrhexis"), and pleomorphism may be prominent. The background is composed of faintly eosinophilic fibrillary material (neuropil) that corresponds to neuritic processes of the neuroblasts. Typically, **rosettes** (Homer-Wright pseudo-rosettes) can be found in which the cells are concentrically arranged about a central space filled with neuropil. Other helpful features include the immunohistochemical detection of **neuron-specific enolase** and ultrastructural demonstration of membrane-bound, cytoplasmic catecholamine-containing secretory granules.

Some neoplasms show signs of **maturation**, either spontaneous or therapy-induced. These tumors have more abundant cytoplasm with large vesicular nuclei and a prominent nucleolus, and they may be found in various stages of maturation, may be found in tumors admixed with primitive neuroblasts (**ganglioneuroblastoma**). Even better differentiated lesions contain many more mature ganglion cells in the absence of residual neuroblasts; such neoplasms are called **ganglioneuroma** (Fig. 7-34B). Maturation of neuroblasts into ganglion cells is usually associated with the appearance of Schwann cells. In fact, the presence of a "schwannian stroma" com-



fascicles of neuritic processes, mature **Schwann cells**, and fibroblasts is a histologic designation of ganglioneuroblastoma and ganglioneuroma; ganglion cells in and of the criteria for maturation.



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 Figure 7-34 **A**, Neuroblastoma. This tumor is composed of small cells embedded in a finely fibrillar matrix (neuropil) arranged concentrically around a central core of neuropil is seen in the upper right corner. **B**, Ganglioneuroma. Maturation of neuroblastomas, are characterized by clusters of large cells with vesicular nuclei and abundant eosinophilic cytoplasm. Ganglion cells. Spindle-shaped Schwann cells are present in the background

## Prognosis

**Table 7-13. Staging of Neuroblastomas**

Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative lymph nodes negative for tumor (nodes adherent to the primary tumor may be positive for tumor).
Stage 2A	Localized tumor with incomplete gross resection; representative ipsilateral nonadherent lymph nodes negative for tumor.
Stage 2B	Localized tumor with or without complete gross excision, ipsilateral nonadherent lymph nodes positive for tumor; representative lymph nodes, which are negative for tumor microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement with contralateral regional lymph node involvement.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other sites (stage 4S).
Stage 4S*	Localized primary tumor (as defined for stages 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow; nucleated cells are constituted by neoplastic cells; >10% involvement of bone marrow is considered stage 4S.

\*S =special.

Adapted from Brodeur GM, et al: The international neuroblastoma staging system. J Clinical Oncol 11:1466, 1993.

Many factors influence prognosis, but the most important are the stage of the tumor and the age of the child (Table 7-13) assumes great importance in establishing a prognosis. Special note should be taken that the outlook for these patients is excellent, despite the spread of disease. As noted in Table 7-13, stages 1 or 2 but for the presence of metastases, which are limited to liver, skin, and bone marrow have an excellent prognosis with minimal therapy, and it is not uncommon for the primary or metastatic disease to regress. The biologic basis of this welcome behavior is not clear. Age is the other important determinant; children younger than 1 year have a much more favorable outlook than do older children at a comparable stage. In the first 3 years of life, stages 1 or 2, or stage 4S. Morphology is an independent prognostic variable in neuroblastoma; a neuroblastoma with a schwannian stroma and gangliocytic differentiation is indicative of a "favorable" histology. Amplification of MYCN is a molecular event that has profound impact on prognosis. MYCN amplification is found in primary tumors, most in advanced-stage disease; the greater the number of copies, the worse the prognosis. Currently the most important genetic abnormality used in risk stratification of neuroblastic tumors is chromosome 1, gain of the distal long arm of chromosome 17, and overexpression of telomerase. Expression of TrkA, a high-affinity receptor for nerve growth factor that is indicative of differentiative potential, is associated with favorable prognosis.

### Clinical Course

Children younger than 2 years with neuroblastomas generally present with protuberant abdomen and weight loss. In older children the neuroblastomas may remain unnoticed until metastases cause pain. Neuroblastomas may metastasize widely through the hematogenous and lymphatic systems in addition to the bone marrow. In neonates, disseminated neuroblastomas may present with multiple skin discoloration to the skin (earning the rather unfortunate moniker of "blueberry muffin baby"). As stated above, many factors influence the prognosis of neuroblastomas, but as a rule of thumb, stage and age are the paramount factors. Stages that occur in infants, as well as low-stage tumors in older children, are usually associated with a better outcome. Tumors in children >1 year of age have the poorest outcome. About 90% of neuroblastomas, regardless of stage, secrete catecholamines (similar to the catecholamines associated with pheochromocytomas), which are associated with elevated blood levels of catecholamines and elevated urine levels of catecholamine metabolites such as homovanillic acid [HVA]. Despite the elaboration of catecholamines, hypertension is much less frequent in neuroblastomas than in pheochromocytomas (Chapter 20).

### SUMMARY

**Neuroblastoma** Neuroblastomas and related tumors arise from neural crest cells in the sympathetic ganglia and adrenal medulla. Neuroblastomas are undifferentiated tumors. Ganglioneuroblastomas and ganglioneuromas demonstrate evidence of differentiation.



stroma and ganglion cells). Homer-Wright pseudo-rosettes are characteristic and stage are the most important prognostic features; infants usually have a better prognosis than older children, while children with higher stage tumors fare worse. Neuroblastoma produces catecholamines, whose metabolites (VMA/HVA) can be used for screening.

### **Retinoblastoma**

Retinoblastoma is the most common malignant eye tumor of childhood. From a pathologic as well as clinical perspective, it is unusual in several aspects when compared with most other solid tumors. Retinoblastoma frequently is *multifocal* and *bilateral*, it undergoes *spontaneous regression*, and patients have a high incidence of second tumors. The incidence decreases with age, most cases being diagnosed before the age of 4 years.

Retinoblastomas occur in both familial and sporadic patterns. *Familial cases typically develop multifocal and bilateral tumors*. All of the sporadic nonheritable tumors are unilateral and unifocal. Patients with familial retinoblastoma are also at increased risk for developing *osteosarcoma* and other soft tissue tumors.

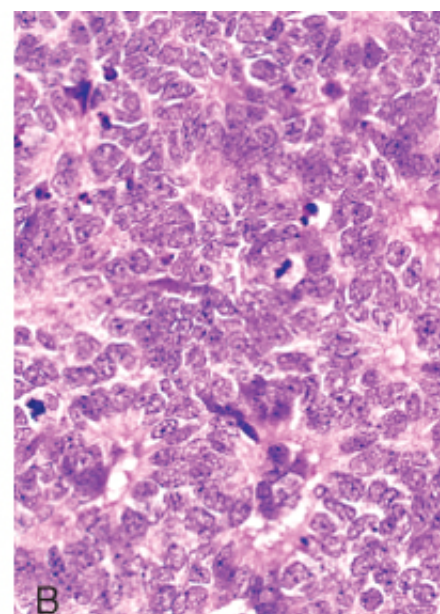
Approximately 60% to 70% of the tumors are associated with a germline mutation in the *RB1* gene. About 30% to 40% of the tumors develop sporadically, and these have somatic *RB1* gene mutations.

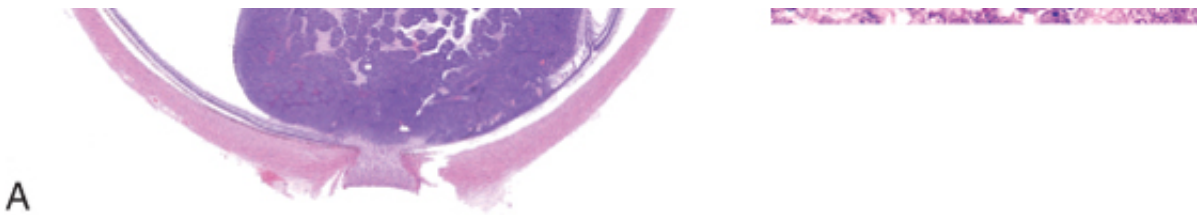
#### **Morphology**

Retinoblastoma is believed to arise from a cell of neuroepithelial origin, usually in the inner nuclear layer (Fig. 35A). The tumors tend to be nodular masses, often with satellite seedings. On light microscopy, undifferentiated areas of these tumors are found to be composed of small, round cells with hyperchromatic nuclei and scant cytoplasm, resembling undifferentiated retinoblastoma.

Differentiated structures are found within many retinoblastomas, the most characteristic being the Flexner and Wintersteiner (**Flexner-Wintersteiner rosettes**). These structures consist of clusters of cuboidal or short columnar cells arranged around a central lumen (Fig. 35B), which is continuous with the lumen of the vitreous body (unlike the **pseudo-rosettes** of neuroblastoma, which lack a central lumen). The nuclei are arranged in a ring around the lumen, which by light microscopy appears to have a limiting membrane resembling the limiting membrane of the retina.

Tumor cells may disseminate beyond the eye through the optic nerve or subarachnoid space. Common sites of distant metastases are the CNS, skull, distal bones, and lymph nodes.





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Figure 7-35 Retinoblastoma. **A**, Note poorly cohesive tumor in retina abutting optic nerve. **B**, Higher power view s and numerous mitotic figures.

### Clinical Features

The median age at presentation is 2 years, although the tumor may be present at birth. The prese strabismus, a whitish hue to the pupil ("cat's eye reflex"), and pain and tenderness in the eye. Unt after early treatment with enucleation, chemotherapy, and radiotherapy, survival is the rule. As no regress, and patients with familial retinoblastoma are at increased risk for developing osteosarcom

### Wilms' Tumor

Wilms' tumor, or *nephroblastoma*, is the most common primary tumor of the kidney in children. Mo 5 years of age. This tumor illustrates several important concepts of childhood tumors: the relation: and increased risk of tumors, the histologic similarity between tumor and developing organ, and fil treatment of childhood tumors. Each of these will be evident from the following discussion.

Three groups of congenital malformations are associated with an increased risk of developing Wil syndrome, characterized by aniridia, genital abnormalities, and mental retardation, have a 33% ch Another group of patients, those with the so-called *Denys-Drash syndrome* (DDS) also has an ext Wilms' tumor. This syndrome is characterized by gonadal dysgenesis and renal abnormalities. Bo abnormalities of the Wilms' tumor 1 (*WT1*) gene, located on chromosome 11p13. The nature of ge Patients with WAGR syndrome demonstrate loss of genetic material (i.e., deletions) of *WT1*, and i negative inactivating mutation in a critical region of the gene. (A dominant negative mutation interl wild-type allele.) The *WT1* gene is critical to normal renal and gonadal development; it is not surp inactivation of one copy of this gene results in genitourinary abnormalities in humans. A third grou *Wiedemann syndrome* (BWS), also has an increased risk of developing Wilms' tumor. These patie organs (e.g., tongue, kidneys, or liver) or entire body segments (hemihypertrophy); enlargement c cytomegaly) is a characteristic microscopic feature. *BWS is an example of a disorder of genomic* that is involved in these patients is in band p15.5 of chromosome 11 distal to the *WT1* locus. Altho second Wilms' tumor locus, the gene involved has not been identified. This region contains at leas from only *one* of the two parental alleles, with transcriptional silencing of the other parental homol *region*, located up-stream of the transcription start site. One of the candidate genes in this region- normally expressed solely from the *paternal allele*, while the maternal allele is imprinted (i.e., siler tumors, *loss of imprinting* (i.e., re-expression of *IGF2* by the maternal allele) can be demonstrated protein, which is postulated to result in both organ enlargement and tumorigenesis. Thus, these a: congenital malformations and tumors represent related manifestations of genetic damage affectin addition to Wilms' tumors, patients with BWS are also at increased risk for developing hepatoblas: rhabdomyosarcomas, and pancreatic tumors.

### Morphology

Grossly, Wilms' tumor tends to present as a large, solitary, well-circumscribed mas bilateral or multicentric at the time of diagnosis. On cut section, the tumor is soft, h gray, with occasional foci of hemorrhage, cystic degeneration, and necrosis (Fig. 7

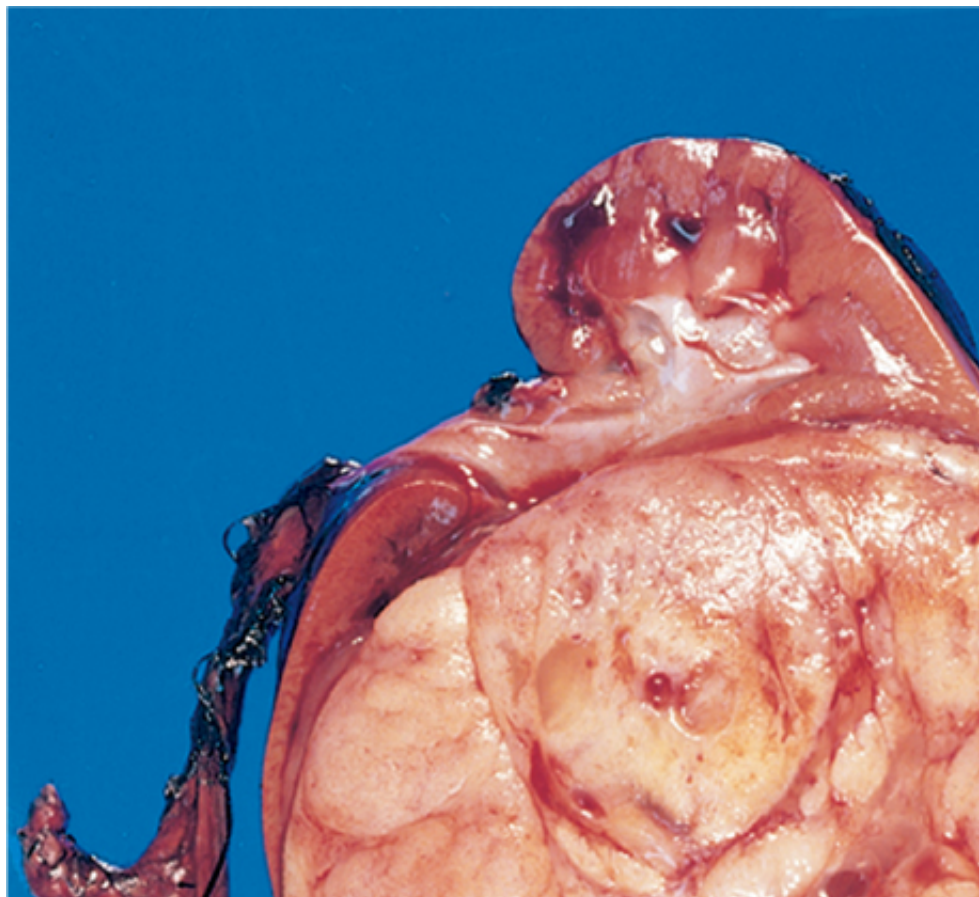
Microscopically, Wilms' tumors are characterized by recognizable attempts to reca nephrogenesis. The classic **triphasic combination** of blastemal, stromal, and epit observed in most lesions, although the percentage of each component is variable (

blue cells, with few distinctive features, characterize the blastemal component. Epi usually takes the form of **abortive tubules or glomeruli**. Stromal cells are usually nature, although skeletal muscle "differentiation" is not uncommon. Rarely, other h identified, including squamous or mucinous epithelium, smooth muscle, adipose tis and neurogenic tissue. Approximately 5% of tumors contain foci of **anaplasia** (cells hyperchromatic, pleomorphic nuclei and abnormal mitoses) (see *inset*, Fig. 7-37). correlates with underlying *p53* mutations, and the emergence of resistance to cher distribution of anaplastic cells within the primary tumor (focal versus diffuse) has in prognosis (see later).

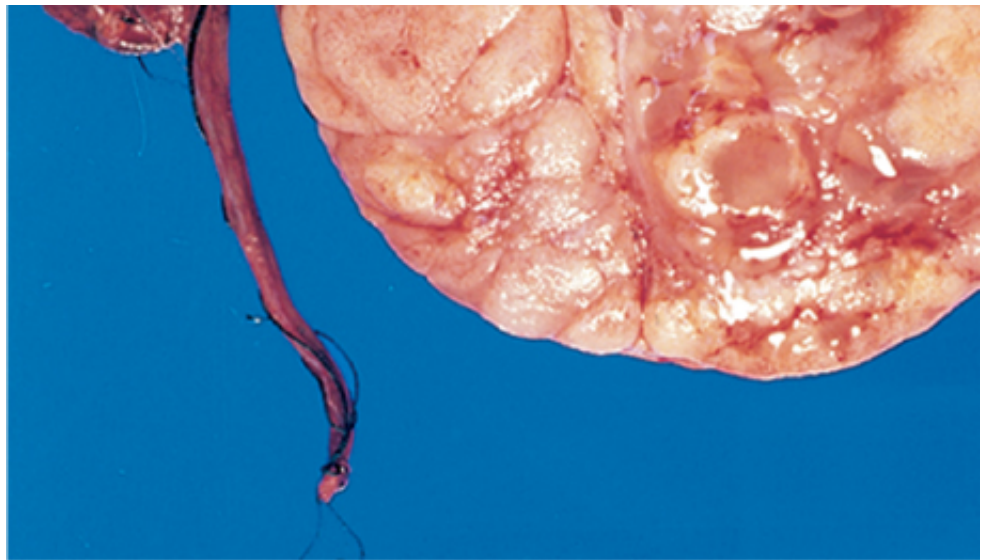
**Nephrogenic rests** are putative precursor lesions of Wilms' tumors and are somet parenchyma adjacent to the tumor. Nephrogenic rests have a spectrum of histolog expansile masses that resemble Wilms' tumors (hyperplastic rests) to sclerotic rest predominantly of fibrous tissue with occasional admixed immature tubules or glomer document the presence of nephrogenic rests in the resected specimen, since these increased risk of developing Wilms' tumors in the **contralateral** kidney.

### *Clinical Course*

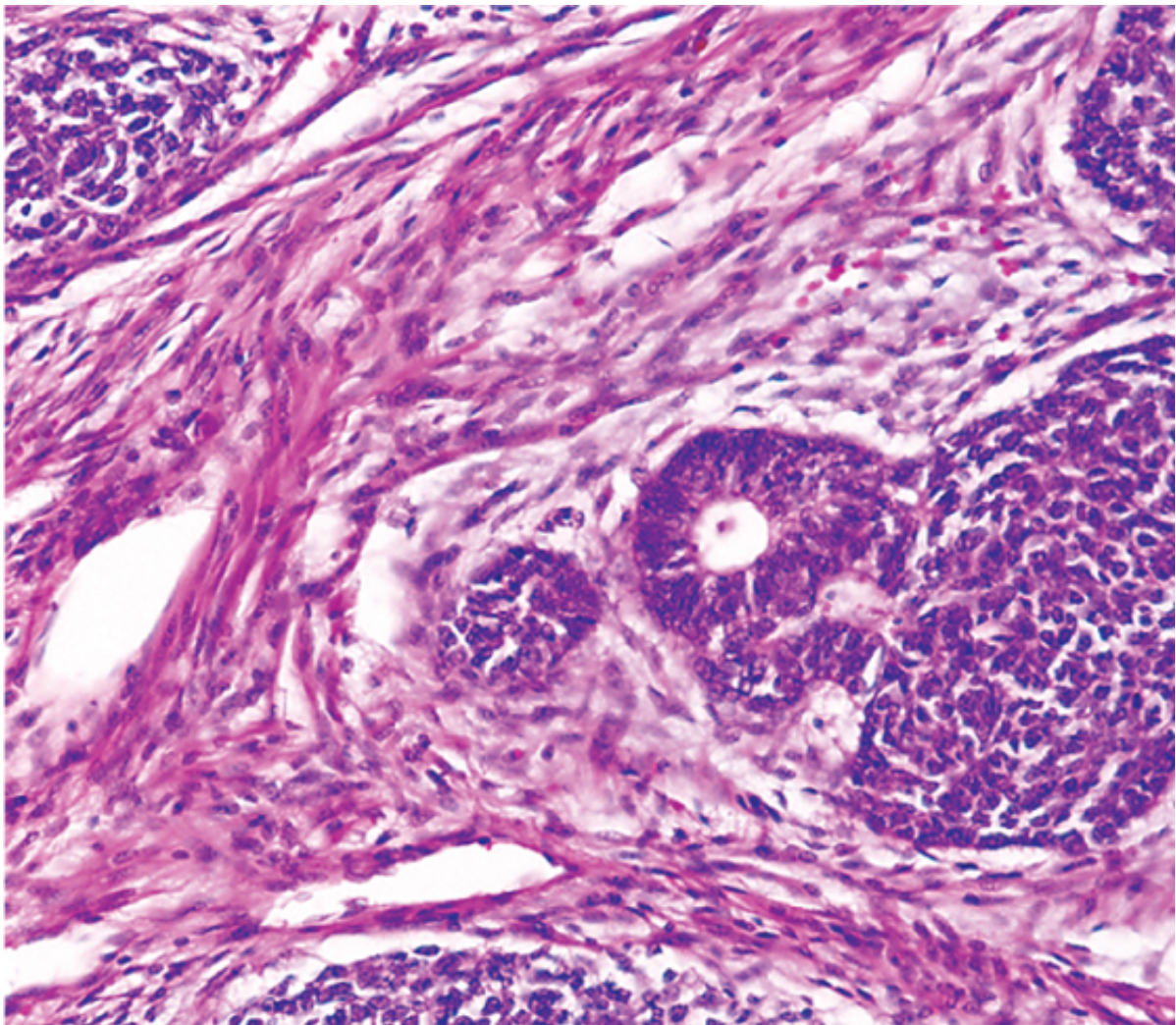
Patients' complaints are usually referable to the tumor's enormous size. Commonly, there is a rea extend across the midline and down into the pelvis. Less often, the patient presents with fever and occasionally, with intestinal obstruction as a result of pressure from the tumor. The prognosis for \ excellent results are obtained with a combination of nephrectomy and chemotherapy. Anaplasia is careful analyses by the National Wilms' Tumor Study group in the United States have shown that confined within the resected nephrectomy specimen, the outcome is no different from tumors with Wilms' tumors with *diffuse anaplasia*, especially those with extra-renal spread, have the least favo correctly identifying this histologic pattern.



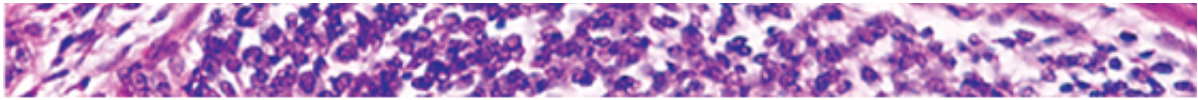




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Figure 7-36 Wilms' tumor in the lower pole of the kidney with the characteristic tan to gray color a







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Figure 7-37 Triphasic histology of Wilms' tumor: the stromal component is composed of spindle-shaped cells in the periphery, the epithelial component is in the center, and the tightly packed blue cells are the blastemal elements. (Courtesy of Dr. J. A. Henson, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX)

## SUMMARY

**Wilms' Tumor** Wilms' tumor is the most common renal neoplasm of childhood. Children with certain syndromes are at increased risk for Wilms' tumors: WAGR, DDS, and BWS associated with *WT1* inactivation, while BWS arises through imprinting abnormalities at the *15q11-q13* locus. The morphologic components of Wilms' tumor include blastema (small round blue cells), epithelial component, and stromal elements. Nephrogenic rests are precursor lesions of Wilms' tumor.



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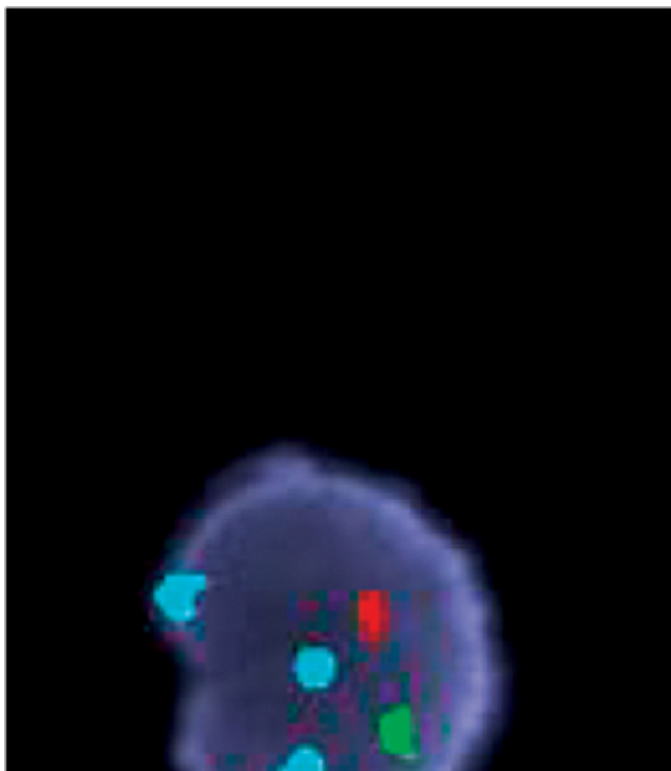
## DIAGNOSIS OF GENETIC DISEASES

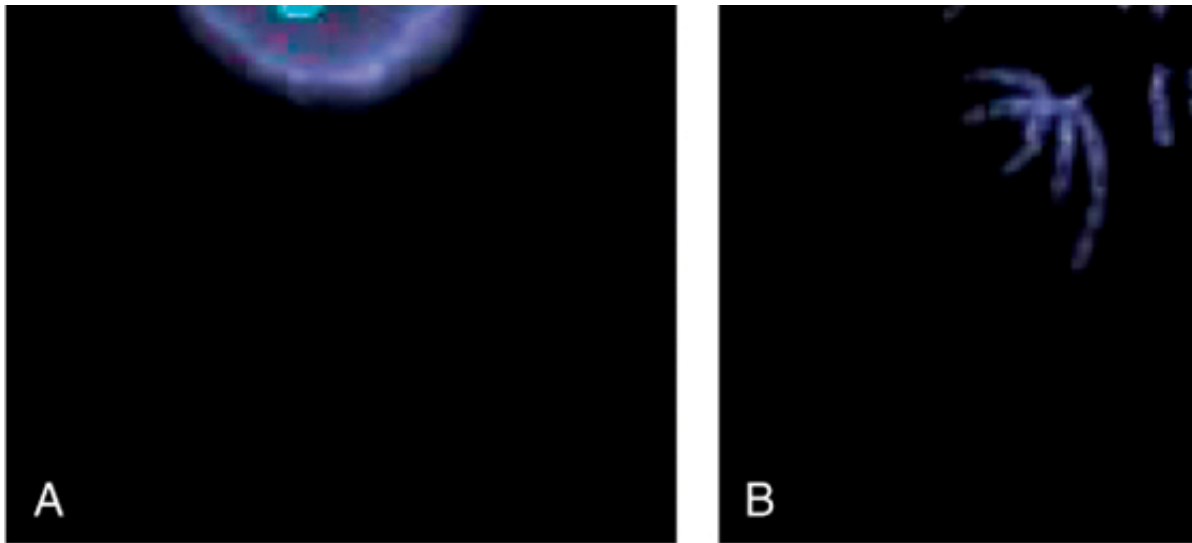
By definition, diseases with a genetic component should have an aberration in the genetic material in the germline (i.e., present in each and every cell of the individual, as with the *CFTR* mutation in cystic fibrosis), or be restricted to specific tissue types or lesions, as with the *MYCN* amplification in neuroblastoma cell lines. The deposition of this sequence in publicly available databases on the Internet has greatly facilitated the identification of disease-causing genes. In this section we will briefly outline some of the traditional and emerging technologies used in the diagnosis of human diseases. Karyotype analysis of chromosomes by G-banding remains the classic approach to detect chromosomal level; however, as one can imagine, the resolution of this technique is fairly low. In addition, it is that it is applicable only to cells that are dividing or can be induced to divide in vitro. To bypass these limitations, FISH and global genomic approaches such as comparative genomic hybridization (CGH) have been developed.

### Fluorescence in Situ Hybridization

FISH utilizes DNA probes that recognize sequences specific to chromosomal regions. The usual resolution is in the megabase ( $1 \times 10^6$  nt), and this defines the limit of resolution of this technique for identifying chromosomal abnormalities. Probes labeled with fluorescent dyes and applied to metaphase spreads or interphase nuclei. The probe hybridizes to the chromosome and thus labels the specific chromosomal region that can be visualized under a fluorescence microscope. FISH to circumvent the need for dividing cells is invaluable when a rapid diagnosis is warranted (e.g., for prenatal diagnosis of a fetus having an underlying genetic disorder). Such analysis can be performed on prenatal samples (e.g., chorionic villus biopsy, or umbilical cord blood), peripheral blood lymphocytes, and even archival tissue. FISH is used for the detection of numeric abnormalities of chromosomes (aneuploidy) (Fig. 7-38A); for the demonstration of complex translocations not detectable by routine karyotyping; for analysis of gene amplification (e.g., in neuroblastomas); and for mapping newly isolated genes of interest to their chromosomal loci.

### Comparative Genomic Hybridization (CGH)





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 Figure 7-38 Fluorescence in situ hybridization (FISH). **A**, Interphase nucleus from a male patient with suspected triploidy. A "FISH cocktail" has been used in which the green probe hybridizes to the X chromosome centromere (one copy), the red probe to the chromosome 18 centromere (three copies), and the aqua probe to the chromosome 18 centromere (three copies). **B**, A metaphase spread in which the green probe hybridizing to chromosome 22q13 region (*green*) and the other hybridizing to chromosome 22q11.2 region (*red*) chromosomes does not stain with the probe for 22q11.2, indicating a microdeletion in this region. This deletion is characteristic of DiGeorge syndrome. (Courtesy of Dr. Nancy R. Schneider and Jeff Doolittle, Cytogenetics Laboratory, University of Texas.)

It is obvious from the preceding discussion that FISH requires prior knowledge of the one or few genes that are suspected of being altered in the test sample. However, chromosomal abnormalities can also be detected without prior knowledge of the specific aberrations that may be present, using a global strategy like CGH. In CGH, the test DNA and a reference (normal) DNA are labeled with different fluorescent dyes (most commonly, Cy5 and Cy3, which fluoresce red and green, respectively). The two labeled DNAs are then hybridized to each other. If the contributions of both samples are equal for a given chromosomal region, then all regions of the genome will fluoresce yellow (due to an equal admixture of green and red dyes). An excess of DNA at any given chromosomal region (such as resulting from an amplification), then results in a shift in the signal from the dye with which this sample was labeled. The reverse will be true in the event of a deletion. Despite having a higher resolution than conventional cytogenetics, CGH cannot detect submicroscopic alterations. Therefore, in recent years, an approach known as *array-based CGH* has been developed. In this approach, segments of genomic DNA are "spotted" on a solid matrix, usually a glass slide. These segments cover the entire genome at regularly spaced intervals, and usually cover all 22 autosomes and the X chromosome. This approach is similar to conventional CGH, except that hybridization of the two differentially labeled samples occurs on the array. This approach allows and deletions in the test sample can now be significantly better localized, often up to a 200-kilobase resolution. The use of microarrays using single-nucleotide polymorphisms (SNPs, see below) provide even higher resolution and are being used to uncover copy number abnormalities in a variety of diseases, from cancer to autism.

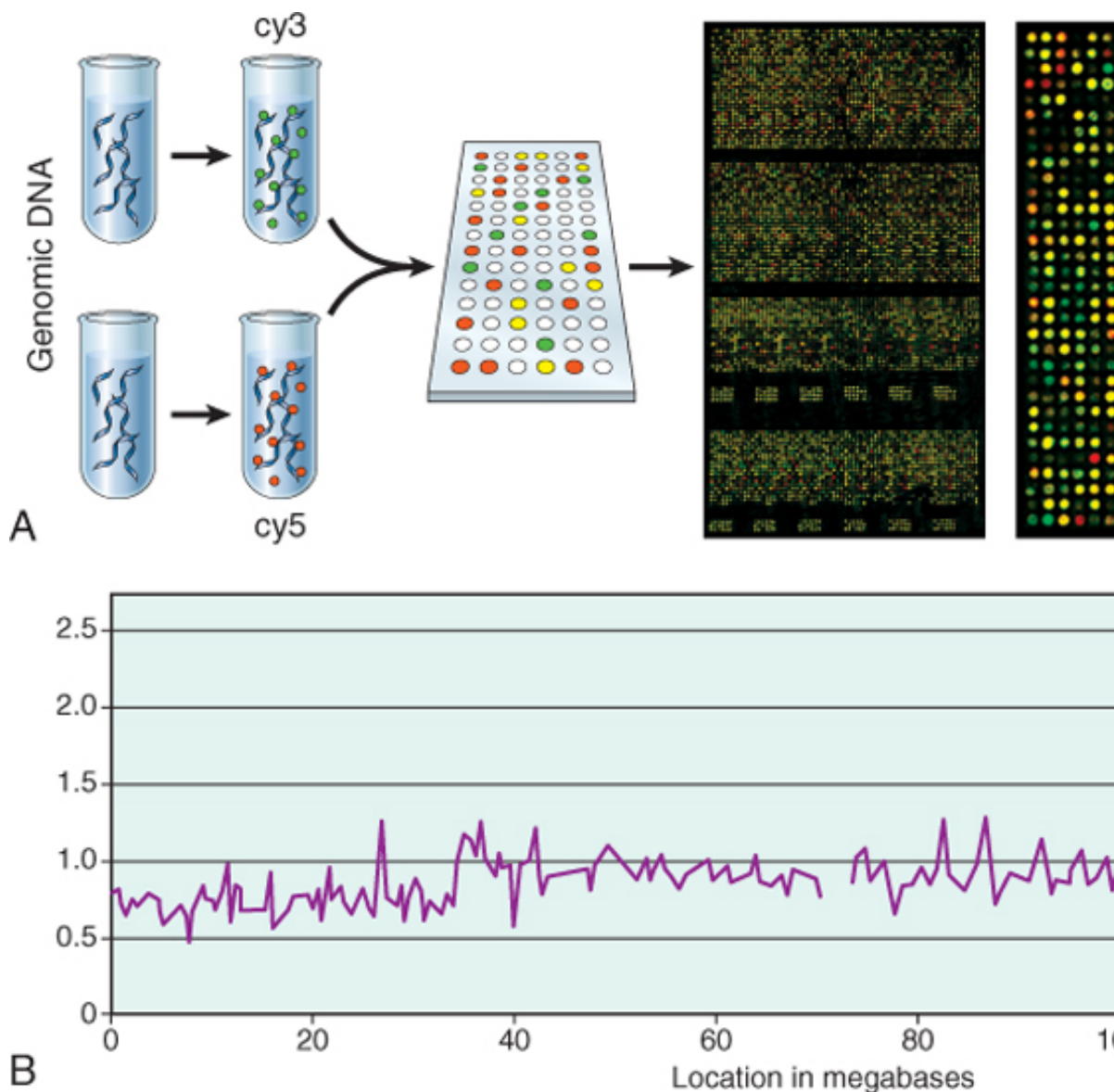
### Molecular Diagnosis of Genetic Disorders

Many genetic diseases are caused by alterations at the nucleotide level (i.e., mutations) that cannot be detected by array-based CGH. In the era predating the ready availability of molecular diagnostic assays, the diagnosis of ("mendelian") disorders depended on the identification of abnormal gene products (e.g., mutant hemoglobin in sickle cell disease) or their clinical effects, such as mental retardation (e.g., in phenylketonuria). Now, it is possible to identify specific mutations and use them as diagnostic tests for an increasing number of genetic disorders. The molecular diagnosis of inherited disorders is often aided by other surrogate techniques:

It is remarkably sensitive. The use of polymerase chain reaction (PCR) allows several milliliters of blood or a few drops of tissue to provide sufficient DNA for PCR amplification. DNA-based tests are not dependent on a gene product or the presence of specialized cells (e.g., brain) or expression of a gene that may occur late in life. Because the DNA for most inherited genetic disorders is present in germline samples, every postzygotic cell carries the same DNA.

These two features have profound implications for the *prenatal diagnosis* of genetic diseases, because they can be obtained from a few milliliters of amniotic fluid or from a biopsy of chorionic villus that can be performed. These two distinct approaches to the molecular diagnosis of single-gene diseases: direct detection of mutations or based on linkage of the disease gene with surrogate markers in the genome. These two methods

### **Direct Detection of DNA Mutations by PCR Analysis**



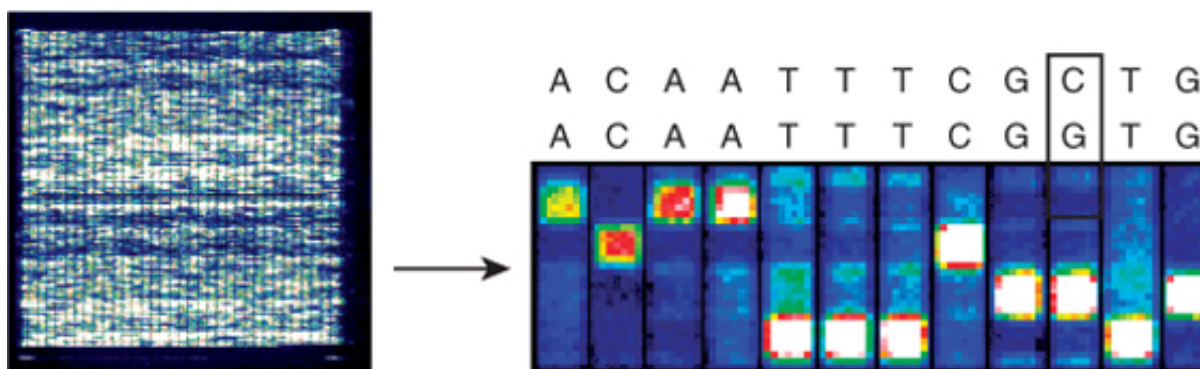
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Figure 7-39 A, Array CGH is performed by hybridization of fluorescently labeled "test" DNA and "control" DNA corresponding to defined chromosomal regions across the human genome. The resolution of most currently available arrays is approximately 100 kb. Higher power view of the array demonstrates copy number aberrations in the "test" sample (Cy5, red), including regions of gain (spots with excess of red signal) and deletion (spots with excess of green signal); yellow spots correspond to regions of normal (diploid) copy number. The data are then digitized resulting in a virtual karyotype of the genome of the "test" sample. In the illustrated example, array CGH identifies a gain in copy number on the distal long arm of chromosome 8, which corresponds to increased copy number of the oncogene *MYC*. (A, From Genome-wide measurement of DNA copy number. Nat Genet 29:263, Web Figure A, Copyright 2001. Reprinted



PCR analysis, which involves exponential amplification of DNA, is now widely used in molecular diagnostics. It is first reverse transcribed to obtain cDNA and then amplified by PCR. This method is often abbreviated as RT-PCR. A major advantage of PCR is that the sequence of the normal gene must be known. To detect the mutant gene, primers at the ends of the normal sequence are designed. By utilizing appropriate DNA polymerases and thermal cycling, the DNA is amplified, producing millions of copies of the DNA sequence between the two primer sites. The sequence can then be performed in several ways:

The DNA can be sequenced to obtain a readout of the order of nucleotides, and by comparing the sequence to the normal sequence, mutations can be identified. The ready availability of automated sequencers has made the traditional Sanger sequencing obsolete, and thousands of base pairs of genomic DNA can now be sequenced. Gene chips (microarrays) have become available that can be used for sequencing genes or DNA (oligonucleotides) that are complementary to the wild-type sequence and to known mutations. On the gene chip, and the DNA sample to be tested is hybridized to the array (Fig. 7-40). By using fluorescent dyes. The hybridization (and consequently, the fluorescent signal emitted) is different for the wild-type sequence if no mutations are present, while the presence of a mutation occurs at the complementary mutant oligonucleotide. Computerized algorithms can then rapidly analyze hundreds of thousands of base pairs of sequence from the fluorescent hybridization pattern to identify mutations. Alternatively, the DNA can be digested with enzymes known as restriction enzymes that recognize specific sequences. If the specific mutation is known to affect a restriction site, then the mutant and normal alleles give rise to products of different sizes. If the mutation affects a restriction site, the mutant and normal alleles give rise to products of different bands on agarose gel electrophoresis. Needless to say, this approach is considered obsolete in the era of automated or array-based sequencing, but remains useful for molecular diagnostics in instances where a mutation occurs at an invariant nucleotide position. Another approach for identifying mutations at a specific site is allele-specific PCR. A 12 mutation in the *KRAS* oncogene that converts glycine<sup>12</sup> [GGT] to aspartic acid [GAT] was detected by adding the nucleotides C and T to the PCR mixture, which are complementary to either the wild-type (GGT) or the mutant (GAT) sequence. Since these two nucleotides are labeled with different fluorophores, the fluorescence emitted by the PCR products is one or another color, depending on whether a "C" or a "T" becomes incorporated in the product. The main advantage of this "allele-specific extension" strategy is that it can detect the presence of mutations in a mixture of normal and abnormal cells (for example, in clinical specimens obtained from patients with cancer). Many variations on this theme have been developed and are being currently used in both laboratory and clinical settings. PCR analysis is also very useful when a mutation is associated with a change in the number of repeats (Fig. 42). As discussed earlier, several diseases, such as the fragile X syndrome, are associated with expansions of DNA that bind to a sequence at the 5' end of the *FMR1* gene, which is affected by trinucleotide repeat expansions. Because there are large differences in the number of repeats, the size of the DNA of normal individuals and those with premutation is quite different. These size differences can be detected by the migration of the amplified DNA products on a gel.

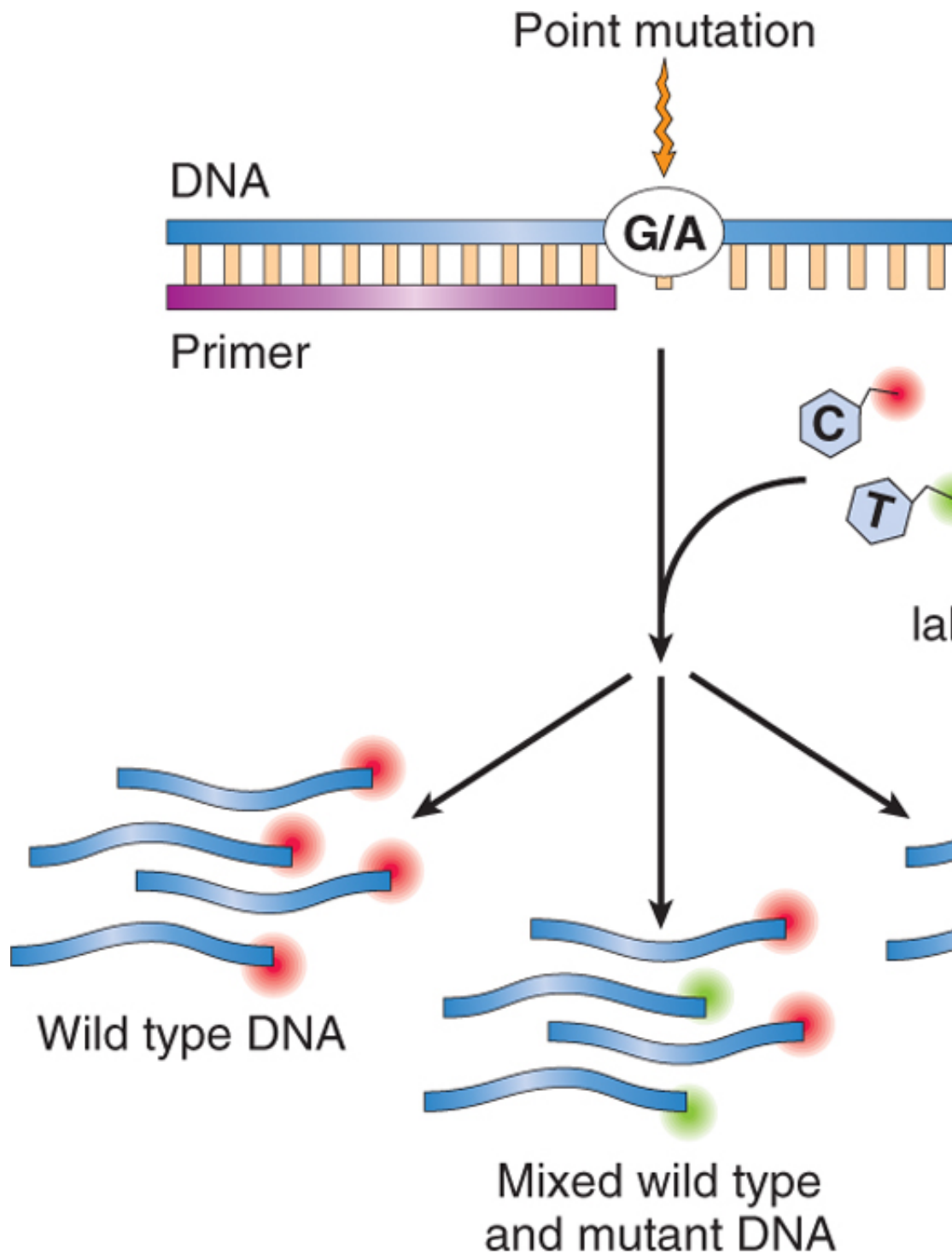


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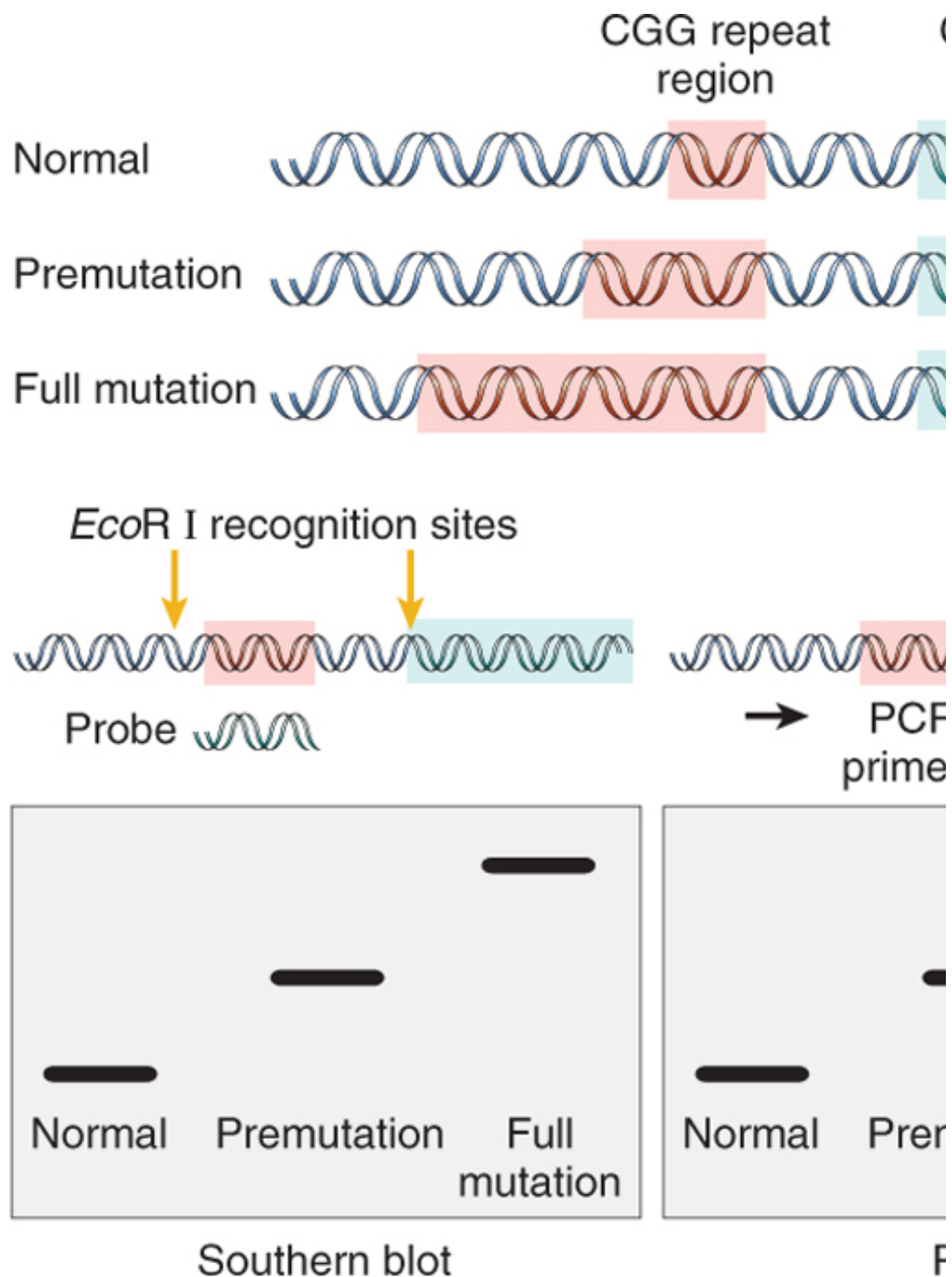
Figure 7-40 Microarray-based DNA sequencing. **Left panel**, A low-power digitized scan of a "gene chip" that is used for sequencing thousands of base pairs of DNA. High-throughput microarrays have been used for sequencing whole genomes (the mitochondria), and entire human chromosomes. **Right panel**, A high-resolution view of the gene chip illustrates the individual hybridization patterns of DNA sequence. Typically, a computerized algorithm is available that can convert the individual hybridization patterns into a sequence of nucleotides. "Sequencing" technologies would require days to weeks for such

data within a matter of minutes (conventional sequencing technologies would require days to weeks for such reference (wild-type) sequence, while the lower one correspond to the test sample sequence. As shown, the comparison in the test sample. (Adapted from Maitra A, et al.: The Human MitoChip: a high-throughput sequencing microarray. Res 14:812, 2004.)

### Linkage Analysis



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Figure 7-41 Allele-specific PCR for mutation detection in a heterogeneous sample containing an admixture of normal to the mutant and wild-type nucleotides at the queried base position are labeled with different fluorophores, such that yields fluorescent signals of varying intensity based on the ratio of mutant to wild-type



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 Figure 7-42 Molecular diagnosis of triplet-repeat expansion in fragile X syndrome. With PCR, the differences in premutation give rise to products of different sizes and mobility. With a full mutation the region between the primers In Southern blot analysis, the DNA is cut by enzymes that flank the CGG repeat region and is then probed with a [ single small band is seen in normal males, a band of higher molecular weight in males with premutation, and a very mutation.

Direct diagnosis of mutations is possible only if the gene responsible for a genetic disorder is known. In several diseases that have a genetic basis, including some common disorders, direct genetic diagnosis of the causal gene has not been identified or because the disease is multifactorial (polygenic) and no surrogate markers in the genome, also known as marker loci, must be used to localize the chromosomal linkage to one or more putative disease-causing genes. *Linkage analysis* deals with assessing the linkage of the disease or trait of interest, with the assumption that marker loci very close to the disease are in the pedigree. With time it becomes possible to define a "disease haplotype" based on a panel of marker loci putative disease allele. Eventually, linkage analysis facilitates localization and cloning of the disease gene. Linkage studies are naturally occurring variations in DNA sequences known as *polymorphisms*. DNA has approximately one nucleotide in every ~1000-base pair stretch. These single nucleotide polymorphisms (SNPs) are found throughout the genome (e.g., in exons and introns and in regulatory sequences). SNPs serve both as a physical marker whose transmission can be followed from parent to child. Because of their prevalence and stability, SNPs can be used in linkage analysis for identifying haplotypes associated with disease. In the last decade, SNPs have become the genetic marker of choice for the study of complex genetic diseases. Some associations between specific SNPs and multifactorial diseases such as hypertension, heart disease, and diabetes. As many as half a million SNPs across the human genome are now available and provide a resolution for linkage analysis at a resolution previously inconceivable. Recently, an international consortium to map the human genome in different ethnic backgrounds (the "HapMap" project) completed its task; the public availability of disease-associated haplotypes and subsequent localization of genes responsible for a host of diseases.

### Indications for Genetic Analysis

In the preceding discussion we described some of the many techniques available today for the diagnosis of genetic disorders. judiciously utilize these methods it is important to recognize which individuals require genetic testing. Genetic testing is divided into prenatal and postnatal analysis. It may involve conventional cytogenetics, FISH, molecular biology, and these techniques.

*Prenatal genetic analysis* should be offered to all patients who are at risk of having cytogenetically abnormal cells obtained by amniocentesis, on chorionic villus biopsy material, or on umbilical cord blood. Indications for prenatal genetic analysis are as follows:

- A mother of advanced age (>34 years), because of greater risk of trisomies
- A parent who is a carrier of a chromosomal translocation, Robertsonian translocation, or inversion (in these cases the gametes may be abnormal and the offspring would be at risk for chromosomal disorders)
- A parent with a previous child with a chromosomal disorder
- A parent with a previous child with an X-linked genetic disorder (to determine fetal sex).

*Postnatal genetic analysis* is usually performed on peripheral blood lymphocytes. Indications are as follows:

- Multiple congenital anomalies
- Unexplained mental retardation and/or developmental delay (e.g., Down syndrome)
- Suspected unbalanced autosome (e.g., Prader-Willi syndrome)
- Suspected sex chromosome abnormality (e.g., Turner syndrome)
- Suspected fragile X syndrome
- Infertility (to rule out sex chromosomal abnormality)
- Carrier status (to rule out the parents as carriers of balanced translocation; both partners should be evaluated)

In closing, it should be pointed out that the progress in unraveling the genetic basis of human disease is rapid. In the coming years. We all wait in anticipation.

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## 8 Environmental and Nutritional Diseases

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Many diseases can be caused or influenced by environmental factors. Broadly defined, the term "environment" encompasses the outdoor, indoor, and occupational environments in which we live. In each of these environments the air we breathe, the food and water we consume, and the direct exposure to toxic agents are major determinants of the health of the population. Another type of environment pertains more particularly to the individual ("personal environment") and is greatly influenced by the use of tobacco, alcohol ingestion, therapeutic and nontherapeutic drug consumption, diet, and the like. Factors in the personal environment generally have a larger effect on human health than does the ambient environment. The term *environmental diseases* refers to lesions and diseases caused by exposure to chemical or physical agents in the ambient, workplace, and personal environments, including diseases of nutritional origin. Environmental diseases are surprisingly common. The International Labor Organization has estimated that work-related injuries and illnesses kill 1.1 million people per year globally—more deaths than are caused by road accidents and wars combined. Most of these work-related problems are caused by illnesses rather than accidents. The burden of disease in the general population created by nonoccupational exposures to toxic agents is much more difficult to estimate, mostly because of the diversity of agents and the difficulties in measuring dosage and duration of exposures. Whatever the precise numbers, environmental (including nutritional) diseases are major causes of disability and suffering and constitute a heavy financial burden, particularly in developing countries.

Environmental diseases are often considered to be consequences of major disasters, such as the methyl mercury contamination of Minamata Bay in Japan in the 1960s, the exposure to dioxin in Seveso, Italy in 1976, the leakage of methyl isocyanate gas in Bhopal, India, in 1984, the Chernobyl nuclear accident in 1986, and the contamination of Tokyo subways by the organophosphate pesticide sarin. Fortunately, these are unusual and infrequent occurrences. Of major concern are the diseases and injury produced by chronic exposure to relatively low levels of contaminants. Several agencies in the United States set permissible levels of exposure to known environmental hazards (e.g., the maximum level of carbon monoxide in air that is noninjurious or the tolerable levels of radiation that are harmless or "safe"). But a host of variables, such as the complex interaction between various pollutants producing multiplicative effects, as well as the age, genetic predisposition, and different tissue sensitivities of exposed persons, create wide variations in individual sensitivity, limiting the value of establishing rigid "safe levels" for entire populations. Nevertheless, such levels are useful for comparative studies of the effects of harmful agents between specific populations, and for estimating risk of disease in heavily exposed individuals. With this brief overview of the nature and magnitude of the problem, we start by presenting some general comments about mechanisms of toxicity and then consider some of the more important environmental hazards.

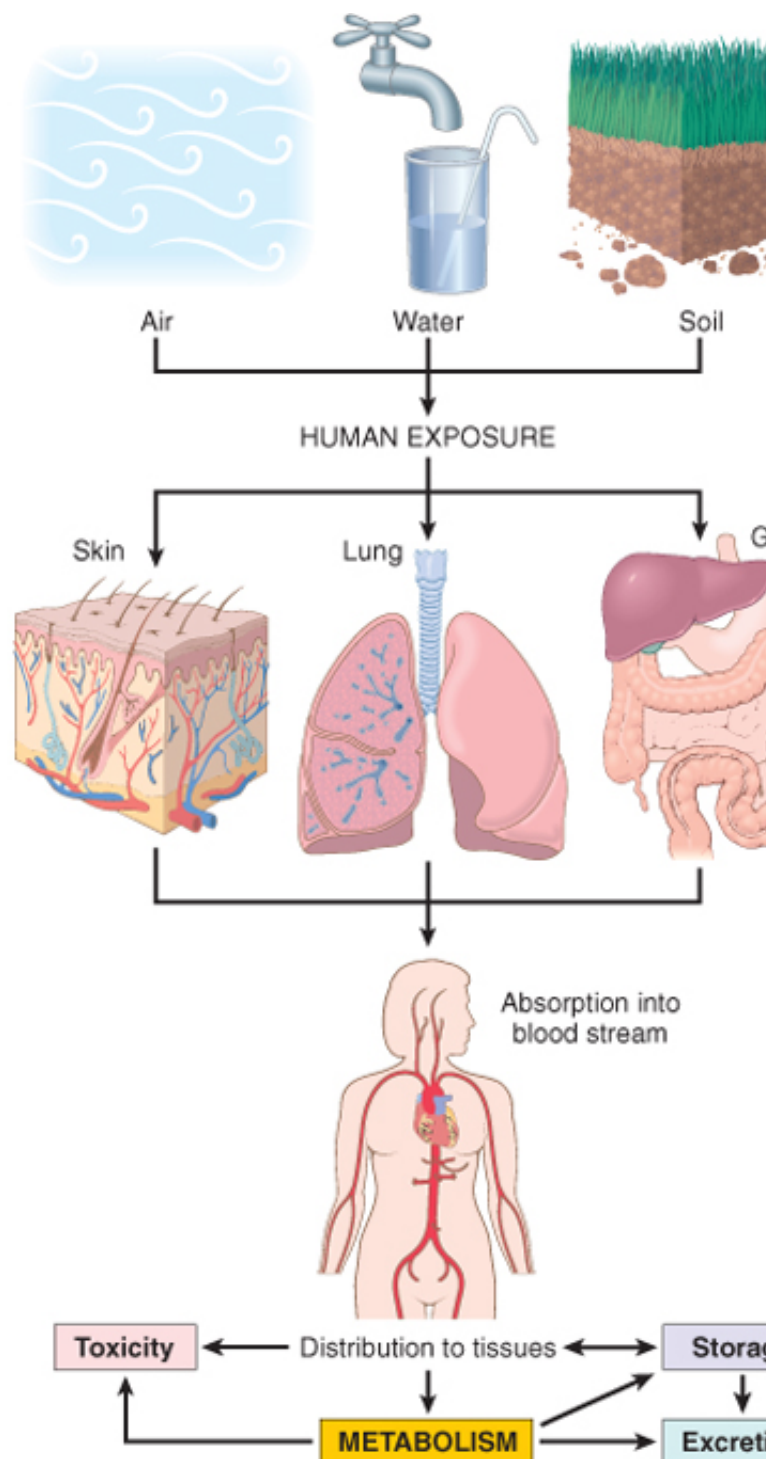


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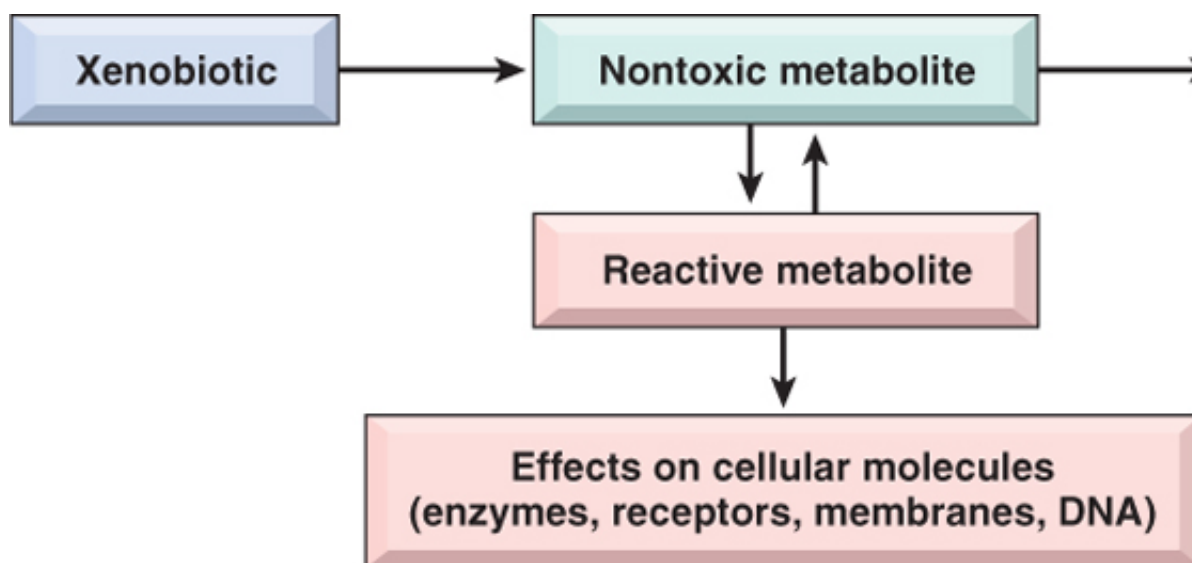
## GENERAL MECHANISMS OF TOXICITY



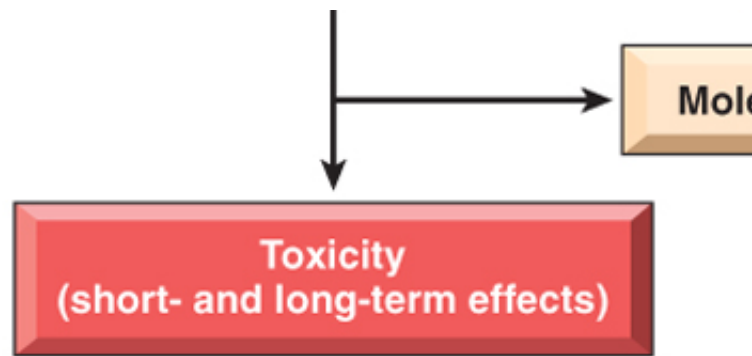
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Figure 8-1 Human exposure to pollutants. Pollutants contained in air, water, and soil are absorbed through the lung, the site of absorption but are generally transported through the bloodstream to various organs, where they may be metabolized, stored, or excreted. Metabolism may result in the formation of water-soluble compounds that are excreted or in activation of the agent.

The number of chemicals available in the United States increases continuously, as the chemical industry produces new synthetic compounds per year. Of approximately 80,000 chemicals in use in the United States, only a small fraction are for health effects. In Europe the number of available chemicals is less than one-half of that in the United States. Chemicals are very high, since many of these chemicals are released in the environment as industrial production wastes. *Toxicology* is defined as the science of poisons. It studies the distribution, effects, and metabolism of chemicals. More broadly, it also includes the study of the effects of physical agents such as radiation and heat. We will focus on the toxicity of exogenous chemicals and drugs.

The *definition of a poison* is not straightforward. It is basically a quantitative concept strictly defined by Paracelsus in the 16th century that "all substances are poisons; the right dosage differentiates between a poison and a medicine." This concept is even more valid today, given the proliferation of therapeutic drugs with potentially harmful side effects. *Xenobiotics* may be present in air, water, food, and soil and are absorbed by inhalation, ingestion, and skin contact (Fig. 8-1). Therapeutic drugs and drugs of abuse may be introduced intravenously, orally, or by other routes. Chemicals may be excreted in urine or feces or eliminated in expired air, or they may be stored in tissues. Chemicals may act at the site of entry, or they may be transported to other sites. Some chemicals are toxic in the body, but most solvents and drugs are metabolized to form water-soluble products (called *toxic metabolites*). Most solvents and drugs are lipophilic, which facilitates their transport in the body through lipid components of cell membranes. The reactions that metabolize xenobiotics into non-toxic or toxic compounds (Figs. 8-1 and 8-2), occur in two phases. In *phase I* reactions, hydrolysis, oxidation, or reduction. Products of phase I reactions are often metabolized into *phase II* reactions of glucuronidation, sulfation, methylation, and conjugation with glutathione, which are readily excreted. The most important component of phase I reactions is the *cytochrome P-450* system, located in the endoplasmic reticulum (ER) of the liver but also present in skin, lungs, and gastrointestinal tract. The system catalyzes reactions that either *detoxify xenobiotics* or *activate xenobiotics into toxic compounds*. Both types of reactions may produce, as a byproduct, *reactive oxygen species (ROS)*, which are discussed in Chapter 1. Examples of metabolic activation of chemicals through the P-450 system include the generation of the toxic trichloromethyl free radical from carbon tetrachloride, and the generation of a DNA adduct (BaP), a carcinogen present in cigarette smoke. The cytochrome P-450 system also participates in the metabolism of a number of common therapeutic drugs such as *acetaminophen*<sup>®</sup>, barbiturates, and anticonvulsants (discussed later in this chapter). There is great variation in the activity of P-450 enzymes as a consequence of *genetic polymorphisms* in cytochrome P-450 enzymes, or it may result from environmental factors. The activity of the enzymes may also be modified by and induced by alcohol consumption and smoking.







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 Figure 8-2 Xenobiotic metabolism. Xenobiotics can be metabolized to nontoxic metabolites and eliminated from the body. However, metabolism may also result in activation of the chemical leading to formation of a reactive metabolite that is toxic to cellular components. Short-term effects develop. (Based on Hodgson E: A Textbook of Modern Toxicology, 3rd ed. Fig. 1-1. Hoboken, NJ: Wiley; 2004.)



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## ENVIRONMENTAL POLLUTION

### Air Pollution

Precious as air is-especially to those deprived of it-it is often laden with many potential causes of disease. Airborne microorganisms have long been major causes of morbidity and mortality. More widespread are the chemical and particulate pollutants found in the air, especially in industrialized nations. Here, we consider these hazards in outdoor and indoor air.

#### Outdoor Air Pollution

The ambient air in industrialized nations is contaminated with an unsavory mixture of gaseous and particulate pollutants, more heavily in cities and in proximity to heavy industry. In the United States the Environmental Protection Agency (EPA) monitors and sets allowable upper limits for six pollutants: sulfur dioxide, carbon monoxide, ozone, nitrogen dioxide, lead, and particulate matter. Together, some of these agents produce the well-known smog that sometimes stifles large cities such as Cairo, Los Angeles, Houston, Mexico City, and São Paulo. It may seem that air pollution is a modern phenomenon. This is not so, since Seneca wrote in AD 61 that he felt an alteration of his disposition soon as he left the "pestilential vapors, soot and heavy air of Rome." The first environmental control was proclaimed by Edward I in 1306 and was straightforward in its simplicity: "whoever should be guilty of burning coal shall suffer the loss of his head." What has changed in modern times is the number and sources of air pollutants, and the types of regulations that control their emission.

**Table 8-1. Health Effects of Outdoor Air Pollutants**

Pollutant	Populations at Risk	Effects
Ozone	Healthy adults and children	Decreased lung function
		Increased airway reactivity
		Lung inflammation
	Athletes, outdoor workers	Decreased exercise capacity
	Asthmatics	Increased hospitalizations
Nitrogen dioxide	Healthy adults	Increased airway reactivity
	Asthmatics	Decreased lung function
	Children	Increased respiratory infections
Sulfur dioxide	Healthy adults	Increased respiratory symptoms
	Patients with chronic lung disease	Increased mortality
	Asthmatics	Increased hospitalization
		Decreased lung function
Acid aerosols	Healthy adults	Altered mucociliary clearance
	Children	Increased respiratory infections
	Asthmatics	Decreased lung function
		Increased hospitalizations
Particulates	Children	Increased respiratory infections
		Decreased lung function
	Patients with chronic lung or heart disease	Excess mortality
	Asthmatics	Increased attacks

Data from Bascom R, et al.: Health effects of outdoor air pollution. Am J Respir Crit Care Med 153(3):477, 1996.

The lungs bear the brunt of the adverse consequences of air pollution, although air pollutants can

The range bear the brunt of the adverse consequences of air pollution, although air pollutants can affect many organ systems (see, for instance, the discussion of lead poisoning and carbon monoxide effects below). Except for some comments here on smoking, pollutant-caused lung diseases are discussed in [Chapter 13](#). Here we comment on the major health effects of ozone, sulfur dioxide, particulates, and carbon monoxide ([Table 8-1](#)).

**Ozone** is one of the most intractable air pollutants, in that levels in many cities exceed the EPA standards. It is a gas formed by sunlight-driven reactions involving nitrogen oxides, which are released mostly by automobile exhaust. Together with oxides and *fine particulate matter*, it forms the familiar "smog" (named for a mixture of smoke and fog). Its toxicity relates to production of free radicals, which injure epithelial cells along the respiratory tract and type I alveolar cells. Low levels of ozone may be well tolerated by healthy individuals but are detrimental to lung function, especially in individuals with asthma or emphysema, and when combined with particulate pollution. Unfortunately, pollutants rarely occur singly but combine to create a veritable "witches' brew."

*Sulfur dioxide, particles, and acid aerosols* are emitted by coal- and oil-fired power plants and industrial processes burning these fuels. Particles are the most important harmful components of these mixtures. Although such particles have not been well characterized chemically or physically, they are considered to be the main cause of morbidity and mortality. Particles that are less than 10  $\mu\text{m}$  in diameter are particularly harmful, since they remain in the airstream to reach the airspaces, where they are phagocytosed by macrophages and neutrophils, causing the release of mediators and inciting a respiratory inflammatory reaction. Larger particles are removed in the nose or are trapped by the mucociliary "escalator."

**Carbon monoxide (CO)** is a nonirritating, colorless, tasteless, odorless gas. It is produced by the imperfect oxidation of carbonaceous materials. Its sources include automotive engines, industries, fossil fuels, home heating with oil (not natural gas), and cigarette smoke. The low levels often found in ambient air may contribute to impaired respiratory function, but by themselves they are not life-threatening. However, individuals working in confined environments with high exposure to fumes, such as tunnel and underground garage workers, may develop chronic poisoning. CO is included here as an air pollutant, but it is also an important cause of accidental and suicidal death. In a small, closed garage, the average car exhaust can induce lethal coma within 5 minutes. CO is a systemic asphyxiant that kills by inducing central nervous system (CNS) depression, which appears so insidiously that victims may not even be aware of their plight and indeed may be unable to help themselves. Hemoglobin has a 200-fold greater affinity for CO than for oxygen. The resultant carboxyhemoglobin is incapable of carrying oxygen. Systemic hypoxia appears when the hemoglobin is 20% to 30% saturated with CO, and unconsciousness and death are probable with 60% to 70% saturation.

## Morphology

**Chronic poisoning** by CO may develop because carboxyhemoglobin, once formed, is remarkably stable and, with low-level persistent exposure to CO, may accumulate to a life-threatening concentration in the blood. The slowly developing hypoxia can insidiously evoke widespread ischemic changes in the CNS; these are particularly marked in the basal ganglia and lenticular nuclei. With cessation of exposure to CO the patient usually recovers, but often there are permanent neurologic sequelae. The diagnosis of CO poisoning is critically dependent on the identification of significant levels of carboxyhemoglobin in the blood.

**Acute poisoning** by CO is generally a consequence of accidental exposure or suicide attempt. In light-skinned individuals, acute poisoning is marked by a characteristic **generalized cherry-red color of the skin and mucous membranes**, resulting from carboxyhemoglobin. If death occurs, depending on the rapidity of onset, morphologic changes may not be present; with longer survival, the brain may be slightly edematous, with punctate hemorrhages and hypoxia-induced neuronal changes. The morphologic changes are not specific:

they simply imply systemic hypoxia. When exposure has not been prolonged, complete recovery is possible; however, sometimes impairments of memory, vision, hearing, and speech remain.

### **Indoor Air Pollution**

As we increasingly "button up" our homes to exclude the environment, the potential for pollution of indoor air increases. The commonest pollutant is tobacco smoke (discussed separately later), but additional offenders are CO, nitrogen dioxide (already mentioned as outdoor pollutants), and asbestos (discussed in [Chapter 13](#)). Only a few comments about some other agents will be made here.

*Wood smoke*, containing various oxides of nitrogen and carbon particulates, is an irritant that predisposes to lung infections and may contain carcinogenic polycyclic hydrocarbons. *Radon*, a radioactive gas derived from uranium, is widely present in soil and in homes. Although radon exposure is an occupational hazard that can cause lung cancer in uranium miners, it does not appear that low level chronic exposures in the home increase lung cancer risk, at least for nonsmokers. *Bioaerosols* include microbiologic agents capable of causing infectious diseases such as Legionnaires' disease, viral pneumonia, and the common cold, as well as less threatening but nonetheless distressing allergens derived from pet dander, dust mites, and fungi and molds that can cause rhinitis, eye irritation and even asthma.

### **SUMMARY**

**Environmental Diseases and Environmental Pollution** Environmental diseases are conditions caused by exposure to chemical or physical agents in the ambient, workplace, and personal environments. Exogenous chemicals known as xenobiotics are absorbed by the body through inhalation, ingestion, and skin contact, and can either be eliminated from the body or accumulate in fat, bone, brain, and other tissues. Xenobiotics can be converted into non-toxic products, or be activated to generate toxic compounds, through a two-phase reaction process that involves the cytochrome P-450 system. The most common air pollutants are ozone, which in combination with oxides and particulate matter forms smog; sulfur dioxide; acid aerosols; and particles of less than 10  $\mu\text{m}$  in diameter. Carbon monoxide is an air pollutant and important cause of death from accidents and suicide; it binds hemoglobin with high affinity and causes systemic asphyxiation with CNS depression.

### **Metals as Environmental Pollutants**

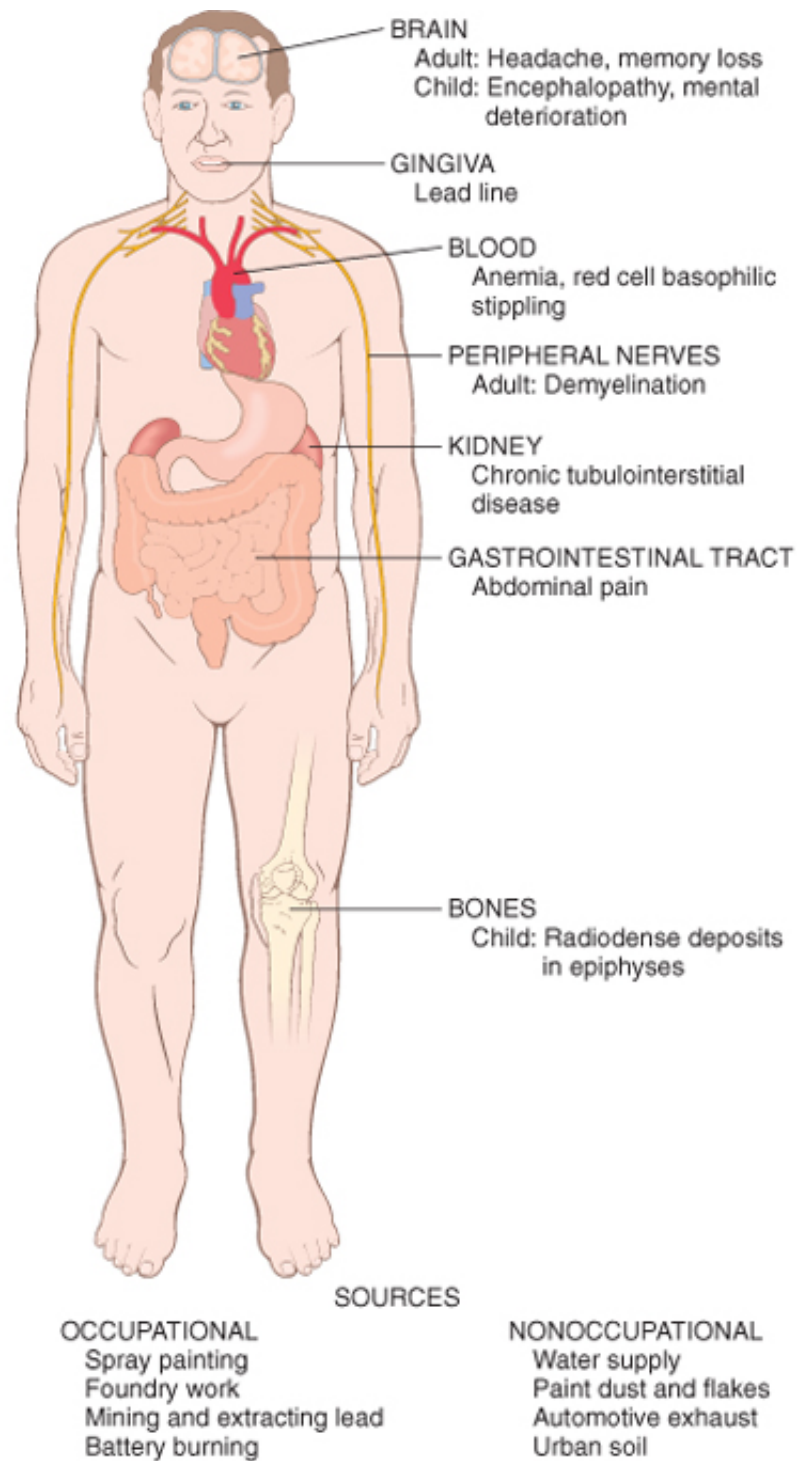
Lead, mercury, arsenic, and cadmium are the heavy metals most commonly associated with harmful effects in human populations and are considered here.

#### **Lead**

Lead exposure occurs through contaminated air and food. For most of the twentieth century the major sources of lead in the environment were lead-containing house paints and gasoline. Although the use of lead-based paints and leaded gas has greatly diminished, lead contamination remains an important health hazard, particularly for children. There are many sources of lead in the environment, such as mines, foundries, batteries, and spray paints, all of which constitute occupational hazards. However, *flaking lead paint* in older houses and soil contamination pose major hazards to youngsters, and ingestion of as much as 200  $\mu\text{g/day}$  may occur. Indeed, a single chip of lead paint the size of a thumbnail may contain 500,000  $\mu\text{g}$  of lead, enough to produce highly toxic levels if completely absorbed. According to the 2005 report from the Centers for Disease Control (CDC), 1.6% of American children had blood lead levels in excess of 10  $\mu\text{g/dL}$  (the maximal allowable level). This percentage decreased from 4.4% in the early 1990s, but lead blood levels in children living in homes containing lead-based paint or lead-contaminated dust generally exceed the maximal allowed levels. Children



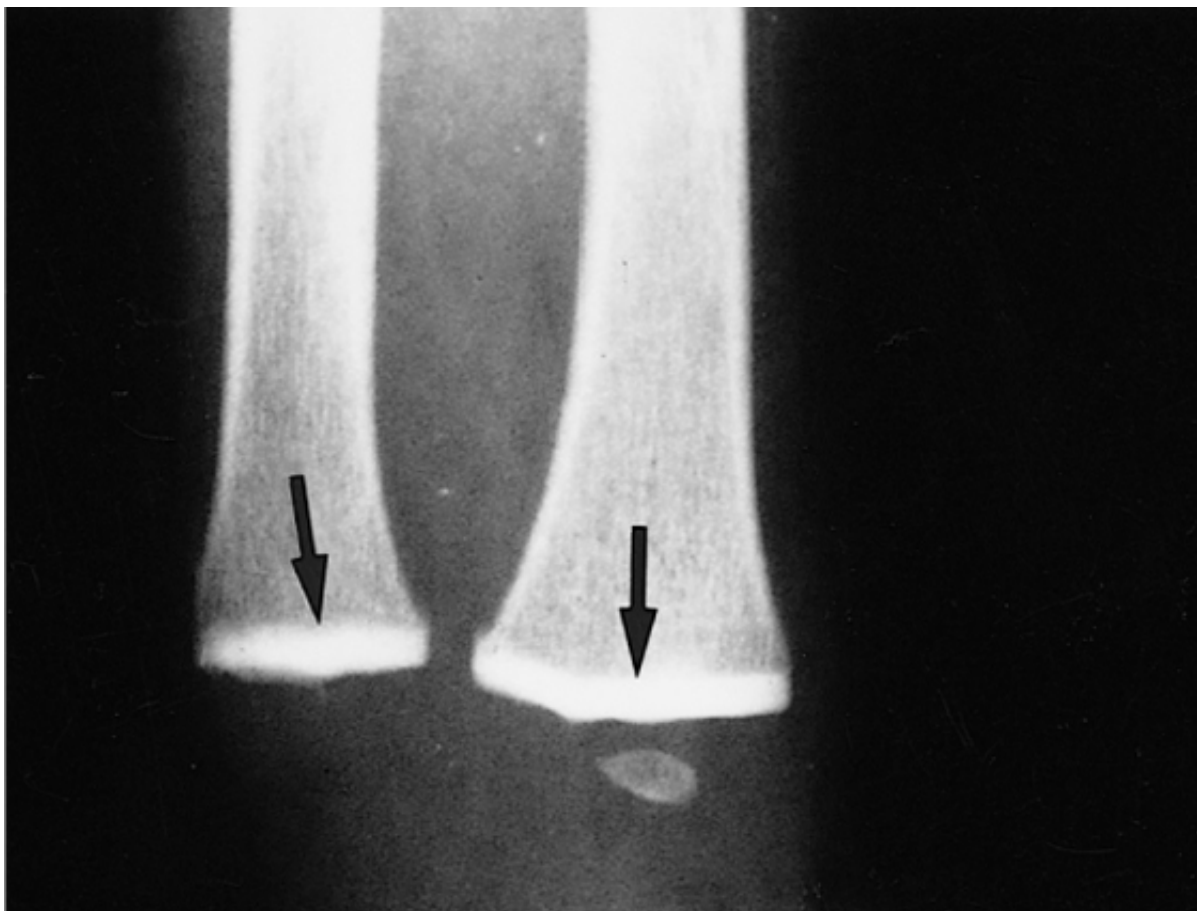
lead-based paint or lead-contaminated dust generally exceed the maximal allowed levels. Children absorb more than 50% of lead from food, while adults may absorb approximately 15%. A more permeable blood-brain barrier in children creates a high susceptibility to brain damage. The main clinical features of lead poisoning are shown in Figure 8-3.

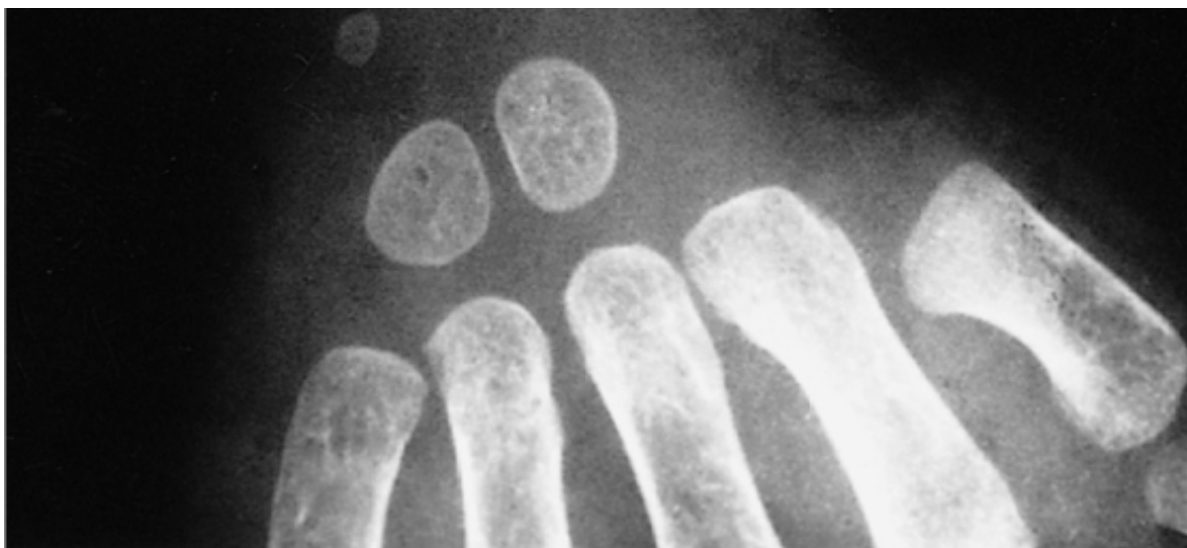


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Figure 8-3 Pathologic features of lead poisoning.

Most of the absorbed lead (80% to 85%) is taken up by bone and developing teeth; lead competes with calcium, binds phosphates, and has a half-life in bone of 20 to 30 years. About 5% to 10% of the absorbed lead remains in the blood, and the remainder is distributed throughout soft tissues. *Excess lead causes neurologic effects in adults and children; peripheral neuropathies predominate in adults while central effects are more common in children.* The effects of chronic lead exposure in children include a lower intellectual capacity manifested by low IQs, as well as behavioral problems such as hyperactivity and poor organizational skills. Lead-induced peripheral neuropathies in adults are generally reversible with elimination of lead exposure, but both peripheral and CNS abnormalities in children are generally irreversible. *Excess lead interferes with the normal remodeling of calcified cartilage* and primary bone trabeculae in the epiphyses in children, causing increased bone density which is detected as radiodense "lead lines" on radiographs (Fig. 8-4). Lead lines of a different sort also occur in the gums, where excess lead stimulates hyperpigmentation of the gum tissue adjacent to the teeth. Lead inhibits the healing of fractures by increasing chondrogenesis and delaying cartilage mineralization. Excretion of lead occurs via the kidneys, and acute exposures may cause damage to proximal tubules.

Lead has a high affinity for sulfhydryl groups and interferes with enzymes involved in heme synthesis (aminolevulinic acid dehydratase and delta ferrochelatase). Iron incorporation into heme is impaired, leading to a *microcytic, hypochromic anemia*. A characteristic finding is *basophilic stippling* of erythrocytes. Lead also inhibits the activity of sodium- and potassium-dependent *adenosine*<sup>®</sup> triphosphatases in cell membranes, an effect that may increase the fragility of red blood cells, causing *hemolytic anemia*. The diagnosis of lead poisoning requires constant awareness of its prevalence and may be suspected on the basis of neurologic changes in children or unexplained anemia with basophilic stippling in red cells. Elevated blood lead and free erythrocyte protoporphyrin levels ( $>50 \mu\text{g/dL}$ ) or, alternatively, zinc-protoporphyrin levels are required for definitive diagnosis. In milder cases of lead exposure, anemia may be the most obvious abnormality detected.





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Figure 8-4 Lead poisoning. Impaired remodeling of calcified cartilage in the epiphyses (arrows) of the wrist has caused a marked increase in their radiodensity, so that they are as radiopaque as the cortical bone. (Courtesy of Dr. G.W. Department of Radiology, University of Texas Southwestern Medical School, Dallas, Texas.)

### Morphology

The major anatomic targets of lead toxicity are the blood, nervous system, GI tract, and kidneys (see [Fig. 8-3](#)).

**Blood changes** resulting from lead accumulation occur fairly early and are characteristic. Lead interferes with normal heme biosynthesis. As a consequence, zinc-protoporphyrin is formed instead of heme. Thus, the elevated blood levels of zinc-protoporphyrin or its product, free erythrocyte protoporphyrin, are important indicators of lead poisoning. Typically, a microcytic, hypochromic, hemolytic anemia appears. Even more distinctive is a punctate **basophilic stippling** of the erythrocytes.

**Brain damage** is prone to occur in children. It may be very subtle, producing mild dysfunction, or it may be massive and lethal. In young children, sensory, motor, intellectual, and psychological impairments have been described, including reduced IQ; learning disabilities; retarded psychomotor development; blindness; and, in more severe cases, psychoses, seizures, and coma. Lead toxicity in the mother may impair brain development in the prenatal infant. The anatomic changes underlying the more subtle functional deficits are ill defined, but there is concern that some of the defects may be permanent. At the more severe end of the spectrum are marked brain edema, demyelination of the cerebral and cerebellar white matter, and necrosis of cortical neurons accompanied by diffuse astrocytic proliferation. In adults, the CNS is less often affected, but frequently a **peripheral demyelinating neuropathy** appears, typically involving the motor innervation of the most commonly used muscles. Thus, the extensor muscles of the wrist and fingers are often the first to be affected, followed by paralysis of the peroneal muscles (**wristdrop** and **footdrop**).

**The GI tract** is also a major source of clinical manifestations. Lead "colic" is characterized by extremely severe, poorly localized abdominal pain.

**Kidneys** may develop proximal tubular damage with intranuclear lead inclusions. Chronic renal damage leads eventually to interstitial fibrosis and

inclusions. Chronic renal damage leads eventually to interstitial fibrosis and possibly renal failure and findings suggestive of gout ("saturnine gout"). Other features of lead poisoning are shown in [Figure 8-3](#).

### **Mercury**

Humans have found many ways to use mercury throughout history, including as a pigment in cave paintings, a cosmetic, a remedy for syphilis, and a component of diuretics. Poisoning from inhaled mercury vapors has long been recognized and is associated with tremor, gingivitis, and bizarre behavior, such as the "Mad Hatter" in Lewis Carroll's *Alice in Wonderland*. Today, the main sources of exposure to mercury are contaminated fish and dental amalgams, which release mercury vapors. In some areas of the world, mercury used in gold mining has contaminated rivers and streams. Inorganic mercury from the natural degassing of the earth's crust or from industrial contamination is converted to organic compounds such as methyl mercury by bacteria. Methyl mercury enters the food chain, and in carnivorous fish such as swordfish, shark, and blue fish, mercury levels may be a million-fold higher than in the surrounding water. The consumption of contaminated fish from the release of methyl mercury in Minamata Bay and the Agano River in Japan, and the consumption of bread containing bread treated with a methyl mercury-based fungicide in Iraq, caused widespread mortality and morbidity. Medical disorders associated with the Minamata episode became known as "*Minamata disease*," and include cerebral palsy, deafness, blindness, and major CNS defects in children exposed in the uterus. *The developing brain is extremely sensitive to methyl mercury*; for this reason, the CDC has recommended that pregnant women reduce to a minimum their consumption of fish known to contain mercury. There has been much publicity about a possible relationship between thimerosal (a compound that contains ethyl mercury, until recently used as a preservative in some vaccines) and the development of autism, but there is little evidence for a relationship between thimerosal and autism.

### **Arsenic**

Arsenic was the favorite poison in renaissance Italy and had some skilled practitioners among the Borgias and Medicis. Deliberate poisoning by arsenic is exceedingly rare today, but exposure to it is an important health problem in many areas of the world. Arsenic is found naturally in soil and water and is used in wood preservatives, herbicides, and other agricultural products. It may be released into the environment from mines and smelting industries. Large concentrations of inorganic arsenic are present in ground water used for drinking in countries such as Bangladesh, Chile, and China. As many as 100 million people in Bangladesh drink water contaminated by arsenic. According to the World Health Organization, this constitutes the highest environmental cancer risk ever found.

The most toxic forms of arsenic are the trivalent compounds [arsenic trioxide<sup>®</sup>](#), sodium arsenite, and arsenic trichloride. If ingested in large quantities, arsenic causes acute toxicity consisting of severe disturbances of the gastrointestinal, cardiovascular and central nervous systems, often progressing to death. These effects may be attributed to the interference with mitochondrial oxidative phosphorylation. Chronic exposure to arsenic causes skin changes consisting of hyperpigmentation and hyperkeratosis. These alterations may be followed by the development of basal and squamous cell carcinomas (including basaloid melanomas). The development of arsenic-induced skin tumors differs from those induced by sunlight, appearing on palms and soles, and by occurring as multiple lesions. Arsenic exposure is also associated with increased risk of the development of lung carcinomas, but the mechanisms of arsenic carcinogenesis in skin and lung have not been elucidated.

### **Cadmium**

By contrast to other metals discussed in this section, cadmium is a relatively modern toxic agent. It is used mainly in nickel-cadmium batteries and is generally disposed of as household waste. It can contaminate soil and plants directly or through fertilizers and irrigation water. Food is the most important source of cadmium exposure for the general population. The health effects of excess cadmium include chronic obstructive lung disease and kidney damage, which initially involves tubular damage that may progress to end-stage renal disease. Cadmium exposure can also cause skeletal abnormalities associated with calcium loss. Cadmium-containing water used to irrigate rice fields in Japan caused a disease in postmenopausal women known as "itai itai" (ouch ouch), which is a combination of



disease in postmenopausal women known as *osteoporosis* (OOST-ee-oh-sis), which is a combination of osteoporosis and osteomalacia, associated with renal disease. A recent survey showed that 5% of the US population aged 20 years and older has urinary cadmium levels that, according to research data, may produce subtle kidney injury and increased calcium loss.

## SUMMARY

**Toxic Effects of Heavy Metals** Lead, mercury, arsenic, and cadmium are the heavy metals most commonly associated with toxic effects in humans. Children absorb more ingested lead than adults; the main source of exposure for children is lead-containing paint. Excess lead causes CNS defects in children and peripheral neuropathy in adults. Excess lead competes with calcium in bones and interferes with the remodeling of cartilage; it also causes anemia. The major source of exposure to mercury is contaminated fish. The developing brain is highly sensitive to methyl mercury, which accumulates in the brain and blocks ion channels. Minamata disease resulting from exposure to high levels of mercury may include cerebral palsy, deafness, and blindness. Arsenic is naturally found in soil and water and is a component of some wood preservatives and herbicides. Excess arsenic interferes with mitochondrial oxidative phosphorylation and causes toxic effects in the GI tract, CNS, and cardiovascular system; long-term exposure causes skin lesions and carcinomas. Cadmium from nickel-cadmium batteries and chemical fertilizers can contaminate soil. Excess cadmium causes obstructive lung disease and kidney damage.

## Industrial and Agricultural Exposures

**Table 8-2. Human Diseases Associated With Occupational Exposures**

Organ/System Effect		Toxicant
Cardiovascular system	Heart disease	Carbon monoxide, lead, solvents, cobalt, cadmium
Respiratory system	Nasal cancer	Isopropyl alcohol, wood dust
	Lung cancer	Radon, asbestos, silica, bis(chloromethyl)ether, nickel, arsenic, chromium, mustard gas
	Chronic obstructive lung disease	Grain dust, coal dust, cadmium
	Hypersensitivity	Beryllium, isocyanates
	Irritation	Ammonia, sulfur oxides, formaldehyde <sub>Rx</sub>
Nervous system	Fibrosis	Silica, asbestos, cobalt
	Peripheral neuropathies	Solvents, acrylamide, methyl chloride, mercury, lead, arsenic, DDT
	Ataxic gait	Chlordane, toluene, acrylamide, mercury
	Central nervous system depression	Alcohols, ketones, aldehydes, solvents
	Cataracts	Ultraviolet radiation
Urinary system	Toxicity	Mercury, lead, glycol ethers, solvents
	Bladder cancer	Naphthylamines, 4-aminobiphenyl, benzidine, rubber products
Reproductive system	Male infertility	Lead, phthalate plasticizers
	Female infertility	Cadmium, lead
	Teratogenesis	Mercury, polychlorinated biphenyls

	teratogenesis	mercury, polychlorinated biphenyls
Hematopoietic system	Leukemia	Benzene, radon, uranium
Skin	Folliculitis and acneiform dermatosis	Polychlorinated biphenyls, dioxins, herbicides
	Cancer	Ultraviolet radiation
Gastrointestinal tract	Liver angiosarcoma	Vinyl chloride

Data from Leigh JP, et al.: Occupational injury and illness in the United States. Estimates of costs, morbidity, and mortality. Arch Intern Med 157:1557, 1997; Mitchell FL: Hazardous waste. In Rom WN (ed): Environmental and Occupational Medicine, 2nd ed. Boston, Little, Brown, 1992, p 1275; and Levi PE: Classes of toxic chemicals. In Hodgson E, Levi PE (eds): A Textbook of Modern Toxicology Stamford, CT, Appleton & Lange, 1997, p 229.

More than 10 million occupational injuries per year occur in the United States, and about 65,000 people die as a consequence of occupational injuries and illnesses. Industrial exposures to toxic agents are varied as the industries themselves. They range from mere irritation of the mucosa of the airways caused by fumes of **formaldehyde** or ammonia, to lung cancer secondary to exposure to asbestos, arsenic, or uranium mining, to leukemia after prolonged exposure to benzene. Human diseases associated with occupational exposures are listed in [Table 8-2](#). Here are a few examples of important agents that contribute to environmental diseases. Toxicity caused by metals has already been discussed in this chapter.

**Organic solvents** are widely used in huge quantities worldwide. Some, such as *chloroform* and *carbon tetrachloride*, are found in degreasing and dry cleaning agents and paint removers. Exposure to high levels of vapors from these agents can cause dizziness and confusion, lead to CNS depression and even coma. Lower levels have toxicity for the liver and kidneys. Occupational exposure of rubber workers to *benzene* and *1,3-butadiene* increases the risk of leukemia. Benzene is oxidized to an epoxide through hepatic CYP2E1, a component of the CYP450 enzyme system already mentioned. The epoxide and other metabolites disrupt cell differentiation in the bone marrow, causing bone marrow aplasia and acute myeloblastic leukemia. **Polycyclic hydrocarbons** may be released from the combustion of fossil fuels, particularly at the high-temperature burning of coal and gas in steel foundries, and are also present in tar and soot. (Pott identified soot as the cause of scrotal cancers in chimney sweeps in 1775, as was mentioned in [Chapter 6](#).) Polycyclic hydrocarbons are among the most potent carcinogens, and industrial exposures have been implicated in the causation of lung and bladder cancer. **Organochlorines**. Organochlorines (and halogenated organic compounds in general) are synthetic products that resist degradation and are lipophilic. Important organochlorines used as pesticides are *DDT* (*dichlorodiphenyltrichloroethane*) and its metabolites, and agents such as **Lindane**, Aldrin, and Dieldrin. Nonpesticide organochlorines include *polychlorinated biphenyls* (*PCBs*) and *dioxin* (*TCDD*; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin). DDT was banned in the United States in 1973, but more than half of the United States population have detectable serum levels of *p,p'*-DDE, a long-lasting DDT metabolite. This substance is found in people 12 through 18 years old who were born after the ban on DDT. PCB and TCDD are also present in the blood of the majority of the population. **Most organochlorines are endocrine disruptors** and have anti-estrogenic or anti-androgenic activity (in experimental work, *p,p'*-DDE blocked androgen binding to its receptor). DDT poisoning in humans causes acute neurologic toxicity. Other health effects for humans have not been firmly established. **Dioxins, PCBs**. These can cause skin disorders such as folliculitis and acneiform dermatosis known as *chloracne*, which consists of acne, comedo formation, hyperpigmentation, and hyperkeratosis, generally around the face and behind the ears. It can be accompanied by abnormalities in the liver and CNS. Because PCBs induce the CYP450 enzyme system, workers exposed to these substances may show abnormal drug metabolism. Environmental disasters in Japan and China in the late 1960s caused by the consumption of rice oil contaminated by PCBs during its production, poisoned about 2000 people in each episode. The primary manifestation of the disease (Yusho in Japan; Yu-Cheng disease in China) was chloracne and hyperpigmentation of the skin and nails. A bizarre case of infant

dioxin poisoning, which made international headlines and was a front-page illustration of chloracne, involved a candidate for office in the Ukraine who developed extensive chloracne systemic symptoms as a consequence of eating a meal spiked with dioxin, offered by one of his "friends." Exposure to *phthalates* in laboratory animals causes endocrine disruption and a testicular dysgenesis syndrome manifested as hypospadias, cryptorchidism, and testicular abnormalities that are similar to conditions of unknown origin found in humans. Phthalates are plasticizers that are widely used in flexible plastics (as in food wraps), and medical containers such as blood and serum bags. A matter of concern is that critically ill infants might receive doses of phthalates from such bags, although effects in humans have not been firmly established. Exposure to *vinyl chloride*, used in the synthesis of polyvinyl resins, was found to cause (in rare individuals) angiosarcoma of the liver, an unusual type of liver tumor. Inhalation of mineral dusts causes chronic, non-neoplastic lung diseases called *pneumoconioses*. This includes diseases induced by organic and inorganic particulates as well as chemical fume-vapor-induced non-neoplastic lung diseases. The most common pneumoconioses are caused by exposures to mineral dust: *coal dust* (mining of hard coal), *silica* (sandblasting, stone cutting), *asbestos* (mining, fabrication, insulation work), and *beryllium* (mining, fabrication). Exposure to these agents nearly always occurs in the workplace. However, the increased risk of cancer as a result of asbestos exposure extends to family members of asbestos workers and to other individuals exposed outside the workplace. Pneumoconioses and their pathogenesis are discussed in [Chapter 13](#).

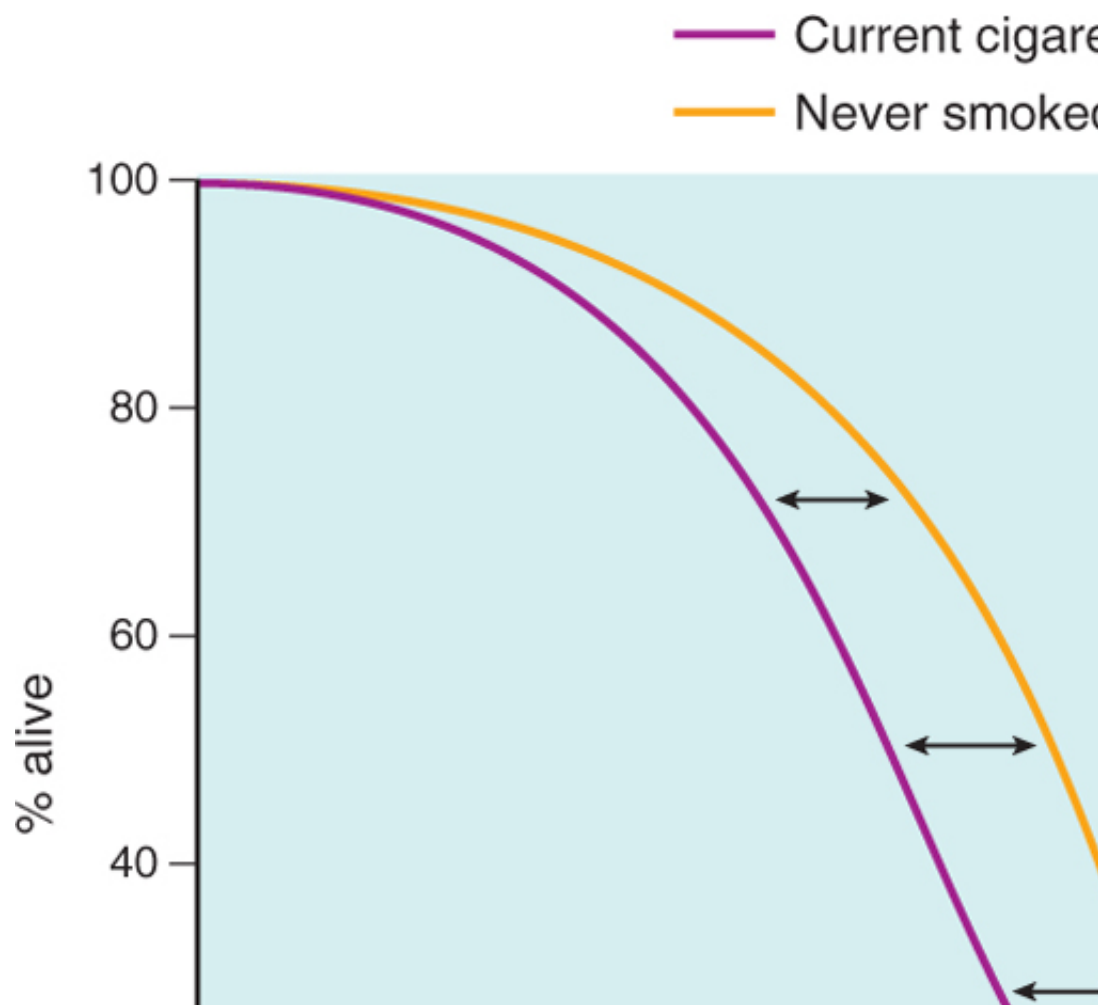




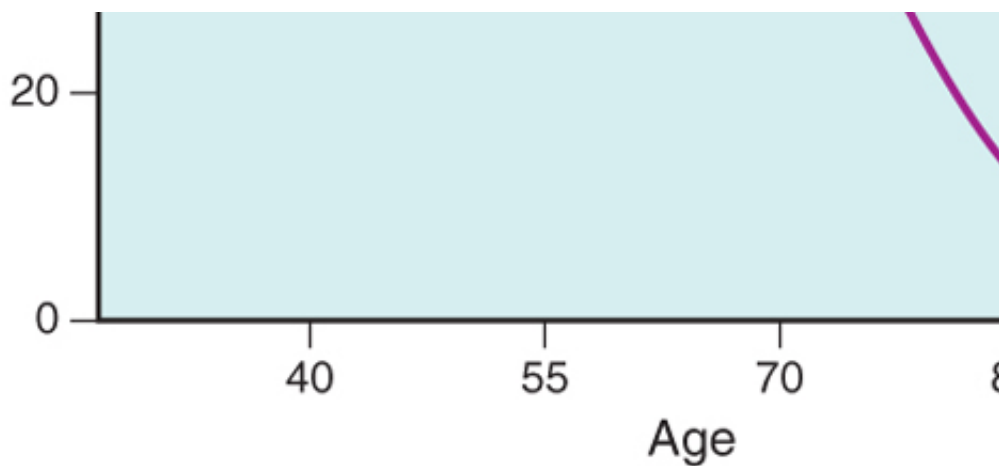
## EFFECTS OF TOBACCO

Tobacco is the most common exogenous cause of human cancers, being responsible for 90% of all lung cancer. It is cigarette smoking, but smokeless tobacco (snuff, chewing tobacco) is also harmful to health and can cause cancer. The use of tobacco products not only creates personal risks, but passive tobacco inhalation ("second-hand smoke") can cause lung cancer in nonsmokers. Cigarette smoking causes, worldwide, about 5 million deaths annually, mostly from cardiovascular disease, various types of cancers, and chronic respiratory problems. By 2020, there will be 8 million tobacco-related deaths yearly, the major increase occurring in developing countries. It is estimated that of the people alive today, approximately 500 million will die from tobacco-related illness. Alone, tobacco is responsible for more than 400,000 deaths per year, one-third of these attributable to lung cancer.

*Smoking is the most preventable cause of human death.* It reduces overall survival, and the impact is seen in many diseases. For instance, while 80% of a population of nonsmokers are alive at age 70, only about 50% of smokers are. *Cessation of smoking greatly reduces the risk of death from lung cancer,* and it even has an effect on other diseases. People who stop smoking at age 60. Unfortunately, the prevalence of smoking is increasing in young people. Recent surveys estimate that 12% of middle-school and 28% of high-school students had used tobacco products before the survey. In the following section we discuss some of the agents contained in tobacco and the health effects of tobacco consumption. Adverse effects of smoking in various organ systems are shown in [Figure 8-1](#).



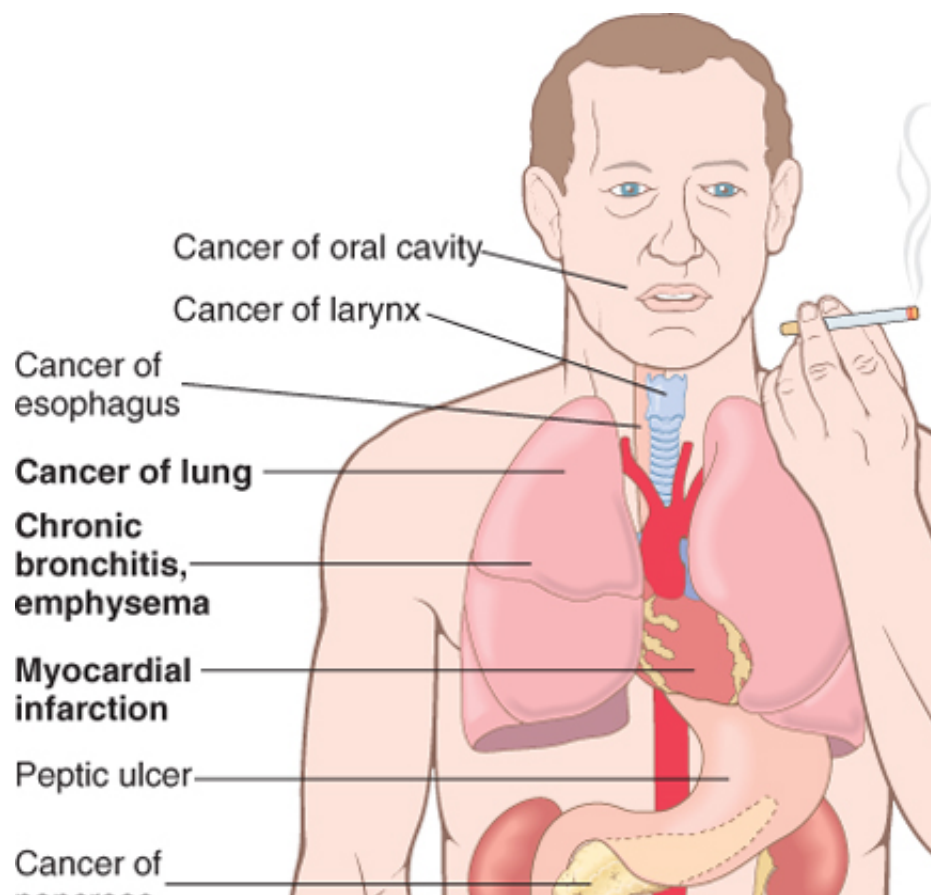


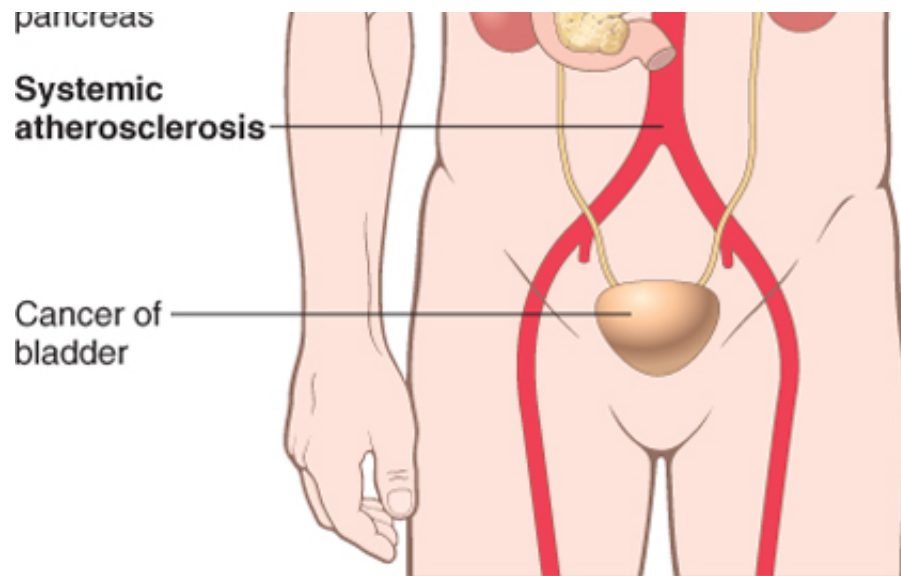


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Figure 8-5 The effects of smoking on survival. The study compared age-specific death rates for current cigarette smokers and never smokers (British Doctors Study). Measured at age 75, the difference in survival between smokers and never smokers was 15 years. (Data from Stewart BW, Kleihues P [eds]: World Cancer Report, Lyon, IARC Press, 2001)

The number of potentially noxious chemicals in tobacco smoke is vast (tobacco contains between 4000 and 6000 chemicals). [Table 8-3](#) provides only a partial list and includes the type of injury produced by these agents. *Nicotine*, found in tobacco leaves, is not a direct cause of tobacco-related diseases, but it is addictive. Without it, it is difficult to stop the habit. *Nicotine* binds to receptors in the brain and, through the release of catecholamines, produces the effects of smoking, such as the increase in heart rate and blood pressure, and the increase in cancer risk. The most common diseases caused by cigarette smoking involve the lung and include emphysema, chronic bronchitis, and lung cancer, all discussed in [Chapter 13](#). Here we briefly mention the mechanisms responsible for some of the other diseases caused by smoking.





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Figure 8-6 Adverse effects of smoking: the more common are in bold face.

Agents in smoke have a direct irritant effect on the tracheobronchial mucosa, producing *inflammation* (bronchitis). Cigarette smoke also causes the recruitment of leukocytes to the lung, with production and subsequent injury to lung tissue, leading to *emphysema*. *Components of cigarette hydrocarbons and nitrosamines (Table 8-4), are potent carcinogens in animals and are most likely lung carcinomas in humans* (see Chapter 13). The risk of development of lung cancer is related to frequently expressed in terms of "pack years" (e.g., one pack daily for 20 years equals 20 pack years per day (Fig. 8-7). Moreover, smoking multiplies the risk of other carcinogenic influences; witness lung carcinomas in asbestos workers and uranium miners who smoke over those who do not smoke tobacco consumption and alcohol in the development of oral cancers mentioned below.

**Table 8-3. Effects of Selected Tobacco Smoke Constituents**

Substance	Effect
Tar	Carcinogenesis
Polycyclic aromatic hydrocarbons	Carcinogenesis
Nicotine <sub>Rx</sub>	Ganglionic stimulation and depression, tumor promotion
Phenol	Tumor promotion; mucosal irritation
Benzopyrene	Carcinogenesis
Carbon monoxide	Impaired oxygen transport and utilization
Formaldehyde <sub>Rx</sub>	Toxicity to cilia; mucosal irritation
Oxides of nitrogen	Toxicity to cilia; mucosal irritation
Nitrosamine	Carcinogenesis

**Table 8-4. Organ-Specific Carcinogens in Tobacco Smoke**

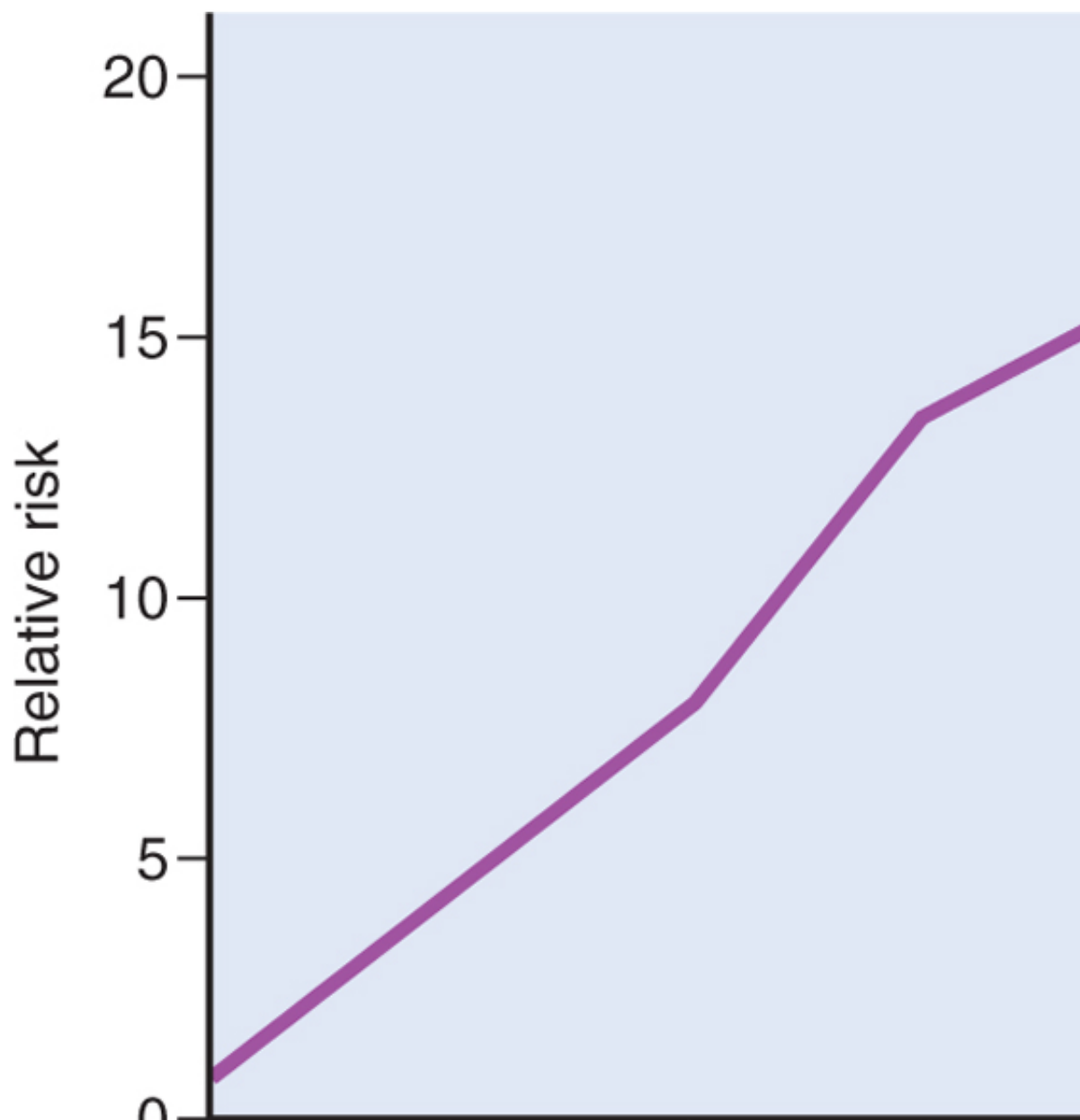
Organ	Carcinogen
Lung, larynx	Polycyclic aromatic hydrocarbons 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanol (NNK) Polonium 210
Esophagus	N'-Nitrosornicotine (NNN)
Pancreas	NNK (?)
Bladder	4-Aminobiphenyl, 2-naphthylamine

Oral cavity (smoking)	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity (snuff)	NNK, NNN, polonium 210

Data from Szczesny LB, Holbrook JH: Cigarette smoking. In Rom WH (ed): Environmental and Occupational Medicine, 2nd ed. Boston: Little Brown, 1997: 101-110.

*Atherosclerosis and its major complication, myocardial infarction, are strongly linked to cigarette smoking.* The mechanisms probably relate to several changes, including increased platelet aggregation, decreased fibrinolysis (because of significant lung disease coupled with the hypoxia related to the CO content of cigarette smoke), increased oxygen demand, and a decreased threshold for ventricular fibrillation. Almost one-third of the population associated with cigarette smoking. Smoking has a multiplicative effect when combined with hypercholesterolemia.

In addition to lung cancers, *tobacco smoke contributes to the development of cancers of the oral cavity and bladder.* Table 8-4 lists organ-specific carcinogens contained in tobacco smoke. Smoke and alcohol in the development of laryngeal cancer. The combination of these agents has a multiplicative effect in developing this tumor (Fig. 8-8).





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Figure 8-7 The risk of lung cancer is determined by the number of cigarettes smoked. (Modified from Stewart B1  
Report, Lyon, IARC Press, 2003.)

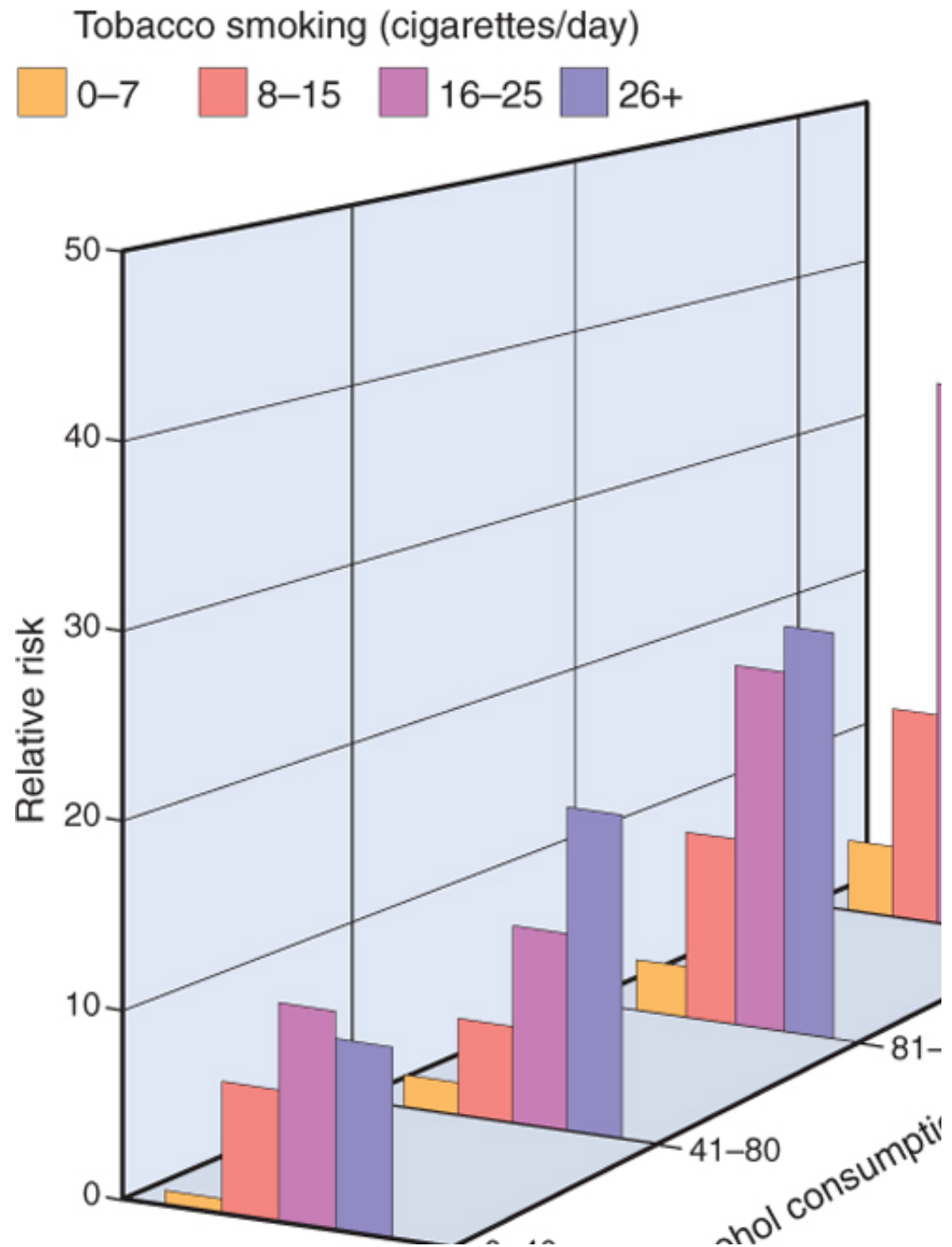


Figure 8-8 Multiplicative increase in the risk of laryngeal cancer from the interaction between cigarette smoking and alcohol consumption. Stewart BW, Kleihues P (eds): World Cancer Report, Lyon, IARC Press, 2003.

*Maternal smoking increases the risk of spontaneous abortions and preterm births* and results in low birth weights (Chapter 7); however, birth weights of infants born to mothers who stopped smoking before pregnancy are normal.

Exposure to *environmental tobacco smoke (passive smoke inhalation)* is also associated with detrimental health effects. It is estimated that the relative risk of lung cancer in nonsmokers exposed to environmental tobacco smoke is 20 times that of nonsmokers who are not exposed to smoke. In the United States, approximately 300 deaths from lung cancer in nonsmokers can be attributed each year to environmental tobacco smoke. Exposure to passive smoke also increases the risk of coronary atherosclerosis and fatal myocardial infarction. Studies report that even low levels of exposure to passive smoke are associated with increased risk of coronary atherosclerosis and fatal myocardial infarction. Children living in a household with a smoker have an increased incidence of respiratory illnesses and asthma. Passive smoke inhalation can be estimated by measuring the blood levels of *cotinine*, a metabolite of *nicotine*. Median cotinine levels in nonsmokers have decreased by more than 60% during the last 10 years, but exposure to environmental tobacco smoke remains a major public health concern, particularly for children. It is clear that the transient pleasure of a puff of smoke is outweighed by the long-term price.

## SUMMARY

**Health Effects of Tobacco** Smoking is the most preventable cause of human cancer. Tobacco smoke contains more than 2000 compounds. Among these are *nicotine*, which is responsible for tobacco addiction and strong carcinogens, mainly polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines. Cigarette smoking is responsible for lung cancers. It also causes cancers of the oral cavity, larynx and pharynx, esophagus and stomach. It is associated with the development of carcinoma of the bladder and kidney and some leukemias. Cessation of smoking reduces the risk of lung cancer. Smokeless tobacco is an important cause of oral cancers. Tobacco consumption interacts with alcohol in multiplying the risk of laryngeal cancer and increases the risk of cancers from occupational exposures to asbestos, uranium, and other agents. Alcohol consumption is an important risk factor for atherosclerosis and myocardial infarction, peripheral vascular disease, and cerebrovascular disease. In the lungs, in addition to causing emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, it increases the risk of abortion, premature birth, and intrauterine growth retardation.







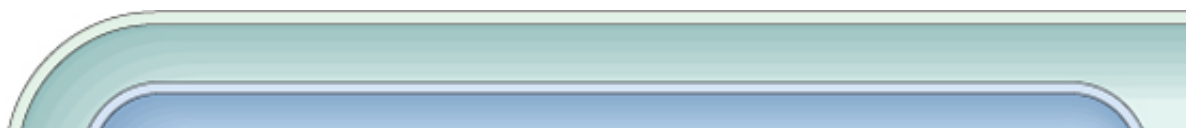
## EFFECTS OF ALCOHOL

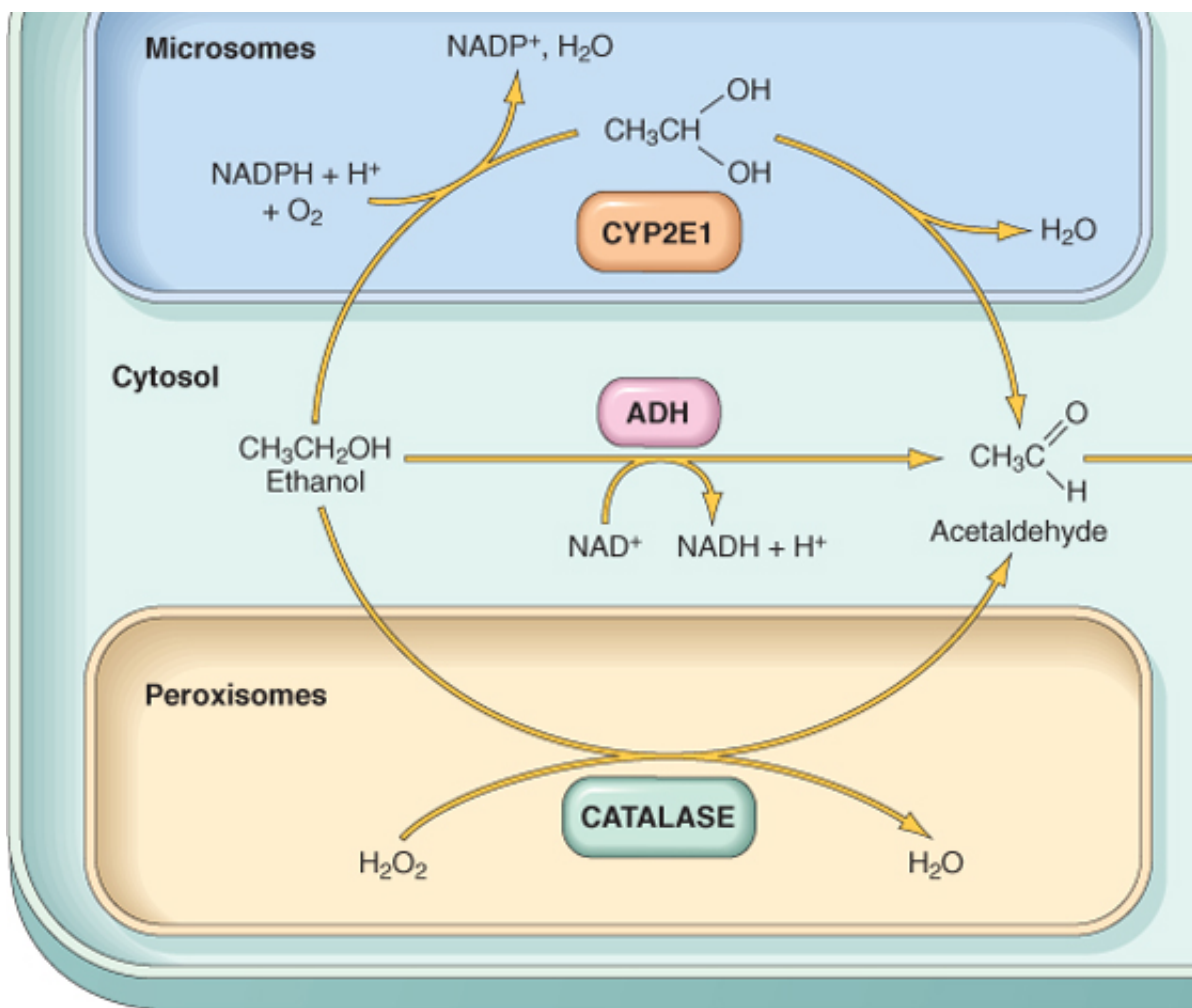
Ethanol is consumed, at least partly, for its mood-altering properties, but when used in moderation is not injurious. When excessive amounts are used, alcohol can cause marked physical and psychological damage. This section describes the lesions directly associated with the abuse of alcohol.

Despite all the attention given to cocaine and heroin addiction, alcohol abuse is a more widespread problem. Fifty percent of adults in the western world drink alcohol, and about 5% to 10% have chronic alcoholism. *More than 10 million chronic alcoholics in the United States and that alcohol consumption is responsible for more than 100,000 deaths each year.* Almost 50% of these deaths result from accidents caused by drunken driving and alcohol-related diseases. Liver disease is a consequence of cirrhosis of the liver. After consumption, ethanol is absorbed unaltered in the small intestine and is distributed to all the tissues and fluids of the body in direct proportion to the blood level. Less than 1% is excreted in sweat, and breath. The amount exhaled is proportional to the blood level and forms the basis of the legal definition of drunk driving. A concentration of 80 mg/dL in the blood constitutes the legal definition of drunk driving. This alcohol concentration may be reached after consumption of about eight bottles of beer (6 to 12 oz each) or 6 ounces of whiskey (about 11 gm of alcohol per ounce). At 300 mg/dL, and coma, with possible respiratory arrest, at higher levels. The rate of metabolism with chronic alcoholism can tolerate levels as high as 700 mg/dL, such tolerance is partially explained by a 5- to 10-fold induction of cytochrome P-450 enzymes in the liver (see discussion below).

Most of the alcohol in the blood is biotransformed to acetaldehyde in the liver by three enzyme systems: alcohol dehydrogenase, cytochrome P-450 isoenzymes, and catalase (Fig. 8-9). Catalase activity, which is of minor importance, because it metabolizes no more than 5% of ethanol in the liver. Acetaldehyde is then converted to acetate by acetaldehyde dehydrogenase, which is then utilized in the citric acid cycle. *The main enzyme system involved in alcohol metabolism is alcohol dehydrogenase, located in the cytosol.* In the blood, alcohol levels, the microsomal ethanol-oxidizing system participates in the metabolism. This system, particularly the CYP2E1 isoform, located in the smooth ER. Induction of P-450 enzymes increases the susceptibility of alcoholics to other compounds metabolized by the same enzyme system, which includes anesthetics, carcinogens, and industrial solvents. Note, however, that when alcohol is present in the blood, it competes with other CYP2E1 substrates and may delay the catabolism of other drugs, thus potentially leading to drug toxicity. We mention only the most important of these.

*Alcohol oxidation by alcohol dehydrogenase causes a decrease in nicotinamide adenine dinucleotide (NADH) (the reduced form of NAD<sup>+</sup>). NAD<sup>+</sup> is required for fatty acid oxidation in the liver. Its deficiency leads to accumulation of fat in the liver of alcoholics. NAD<sup>+</sup> is also required for the conversion of lactate to pyruvate. The NADH/NAD<sup>+</sup> ratio in alcoholics causes metabolic acidosis resulting from lactic acid accumulation, which has deleterious effects and may be responsible for some of the acute effects of alcohol. The efficiency of alcohol metabolism varies among populations, depending on the composition of acetaldehyde dehydrogenase isozymes, and on the activity of the enzyme. About 50% of individuals of Asian background have deficiencies in acetaldehyde dehydrogenase and experience flushing, tachycardia, and hyperventilation after alcohol ingestion. Metabolism of alcohol produces reactive oxygen species and causes lipid peroxidation of cell membranes. Never before, the mechanisms that account for alcohol-induced cellular injury have not been well defined. Alcohol may cause the release of endotoxin (lipopolysaccharide), a product of gram-negative bacteria from the intestinal flora. Endotoxin stimulates the release of tumor necrosis factor (TNF) and other cytokines from circulating macrophages and from Kupffer cells.*





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 Figure 8-9 Metabolism of ethanol: oxidation of ethanol to acetaldehyde by three different routes, and the generative dehydrogenase (ADH) takes place in the cytosol; the cytochrome P-450 system and its CYP2E1 isoform are located in peroxisomes. Oxidation of acetaldehyde by aldehyde dehydrogenase (ALDH) occurs in mitochondria. In Klassen CD [ed]: Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed.

The adverse effects of ethanol can be categorized into its acute effects and the consequences of

*Acute alcoholism* exerts its effects mainly on the CNS, but it may induce hepatic and gastric changes with continued alcohol consumption. Even with moderate intake of alcohol, multiple fat droplets accumulate in the liver (fatty change or hepatic steatosis). The gastric changes are acute gastritis and ulceration. In the cerebellum, there is stimulation and disordered cortical, motor, and intellectual behavior. At progressively higher doses, lower medullary centers are depressed, including those that regulate respiration. Respiratory arrest

*Chronic alcoholism* is responsible for morphologic alterations, primarily in the liver and stomach, kidneys, and tissues. Chronic alcoholics suffer significant morbidity and have a shortened life span, related to liver disease, GI tract, CNS, cardiovascular system, and pancreas.

The liver is the main site of chronic injury. In addition to fatty change, mentioned above, chronic alcoholism causes hepatitis and cirrhosis, as described in Chapter 16. Cirrhosis is associated with portal hypertension and development of hepatocellular carcinoma. In the GI tract, chronic alcoholism can cause major esophageal varices (associated with cirrhosis), which may prove fatal. Thiamine deficiency

patients; the principal lesions resulting from this deficiency are *peripheral neuropathies* and [Table 8-9](#) and [Chapter 23](#)). Cerebral atrophy, cerebellar degeneration, and optic neuropathy effects on the cardiovascular system. Injury to the myocardium may produce dilated congestive *cardiomyopathy*), discussed in [Chapter 11](#). Moderate amounts of alcohol (one drink per day) levels of high-density lipoproteins (HDL) and inhibit platelet aggregation, thus protecting against heavy consumption, with attendant liver injury, results in decreased levels of HDL, increasing disease. Chronic alcoholism is also associated with an increased incidence of hypertension and of *acute and chronic pancreatitis* ([Chapter 17](#)). The use of ethanol during pregnancy reports cause *fetal alcohol syndrome*. It consists of microcephaly, growth retardation and facial abnormalities in mental functions in older children. It is difficult to establish the amount of alcohol consumed in *alcohol consumption syndrome*, but consumption during the first trimester of pregnancy is particularly harmful. Consumption with an *increased incidence of cancer* of the oral cavity, esophagus, liver, and, possibly, brain. Carcinogenic effect are uncertain. Ethanol is a substantial source of energy (empty calories), and deficiencies, particularly of the B vitamins.

## SUMMARY

**Alcohol-Metabolism and Health Effects** Acute alcohol abuse causes drowsiness at approximately 200 mg/dL. Stupor and coma develop at higher levels. Alcohol is metabolized to acetaldehyde in the liver by alcohol dehydrogenase, by the cytochrome P-450 2E1, and by catalase, which is of minor importance. Acetaldehyde is converted to acetate and utilized in the respiratory chain. Alcohol oxidation by alcohol dehydrogenase leads to accumulation of fat in the liver and metabolic acidosis. The main effects of chronic alcohol consumption are fatty liver, alcoholic hepatitis, and cirrhosis, which causes portal hypertension and increases the risk of development of hepatocellular carcinoma. Chronic alcoholism also causes bleeding from gastritis and gastric ulcers, peripheral neuropathy associated with vitamin B1 deficiency, and alcoholic cardiomyopathy, and increases the risk for acute pancreatitis. Chronic alcohol consumption is a major risk factor for cancers of the mouth, larynx, and esophagus. The risk is greatly increased by concurrent smoking and tobacco.





## INJURY BY THERAPEUTIC DRUGS AND DRUGS OF ABUSE

### Injury by Therapeutic Drugs (Adverse Drug Reactions)

Adverse drug reactions (ADRs) refer to untoward effects of drugs that are given in conventional therapeutic settings. These reactions are extremely common in the practice of medicine and are believed to affect 7% to 8% of patients admitted to a hospital. About 10% of these prove fatal. [Table 8-5](#) lists common pathologic findings in ADRs and the drugs most frequently involved. As can be seen in the table, many of the drugs involved in ADRs, such as the antineoplastic agents, are highly potent, and the ADR is a calculated risk of the dosage assumed to achieve the maximal therapeutic effect. Commonly used drugs such as long-acting tetracyclines, which are used to treat diverse conditions, including acne, may produce localized or systemic reactions ([Fig. 8-10](#)). Because they are widely used, estrogens and oral contraceptives are discussed next in more detail. In addition, [acetaminophen<sub>Rx</sub>](#) and [aspirin<sub>Rx</sub>](#), which are nonprescription drugs but are important causes of accidental or intentional overdose, merit special comment.

### Exogenous Estrogens and Oral Contraceptives (OCs)

#### Exogenous Estrogens

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**Table 8-5. Some Common Adverse Drug Reactions and Their Agents**

Reaction	Major Offenders
<b>Blood Dyscrasias*</b>	
Granulocytopenia, aplastic anemia, pancytopenia	Antineoplastic agents, immunosuppressives, and <a href="#">chloramphenicol<sub>Rx</sub></a>
Hemolytic anemia, thrombocytopenia	Penicillin, <a href="#">methyldopa<sub>Rx</sub></a> , quinidine
<b>Cutaneous</b>	
Urticaria, macules, papules, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, abnormal pigmentation	Antineoplastic agents, sulfonamides, hydantoins, some antibiotics, and many other agents
<b>Cardiac</b>	
Arrhythmias	<a href="#">Theophylline<sub>Rx</sub></a> , hydantoins
Cardiomyopathy	Doxorubicin, daunorubicin
<b>Renal</b>	
Glomerulonephritis	<a href="#">Penicillamine<sub>Rx</sub></a>
Acute tubular necrosis	Aminoglycoside antibiotics, cyclosporin, <a href="#">amphotericin B<sub>Rx</sub></a>
Tubulointerstitial disease with papillary necrosis	Phenacetin, salicylates
<b>Pulmonary</b>	
Asthma	Salicylates
Acute pneumonitis	<a href="#">Nitrofurantoin<sub>Rx</sub></a>
Interstitial fibrosis	<a href="#">Busulfan<sub>Rx</sub></a> , <a href="#">nitrofurantoin<sub>Rx</sub></a> , bleomycin
<b>Hepatic</b>	
Fatty change	Tetracycline
Diffuse hepatocellular damage	<a href="#">Halothane<sub>Rx</sub></a> , <a href="#">isoniazid<sub>Rx</sub></a> , acetaminophen
Cholestasis	Chlorpromazine, estrogens, contraceptive

	agents
<b>Systemic</b>	
Anaphylaxis	Penicillin
Lupus erythematosus syndrome (drug-induced lupus)	Hydralazine, procainamide
<b>Central Nervous System</b>	
Tinnitus and dizziness	Salicylates
Acute dystonic reactions and parkinsonian syndrome	Phenothiazine antipsychotics
Respiratory depression	Sedatives

\*Feature of almost half of all drug-related deaths.

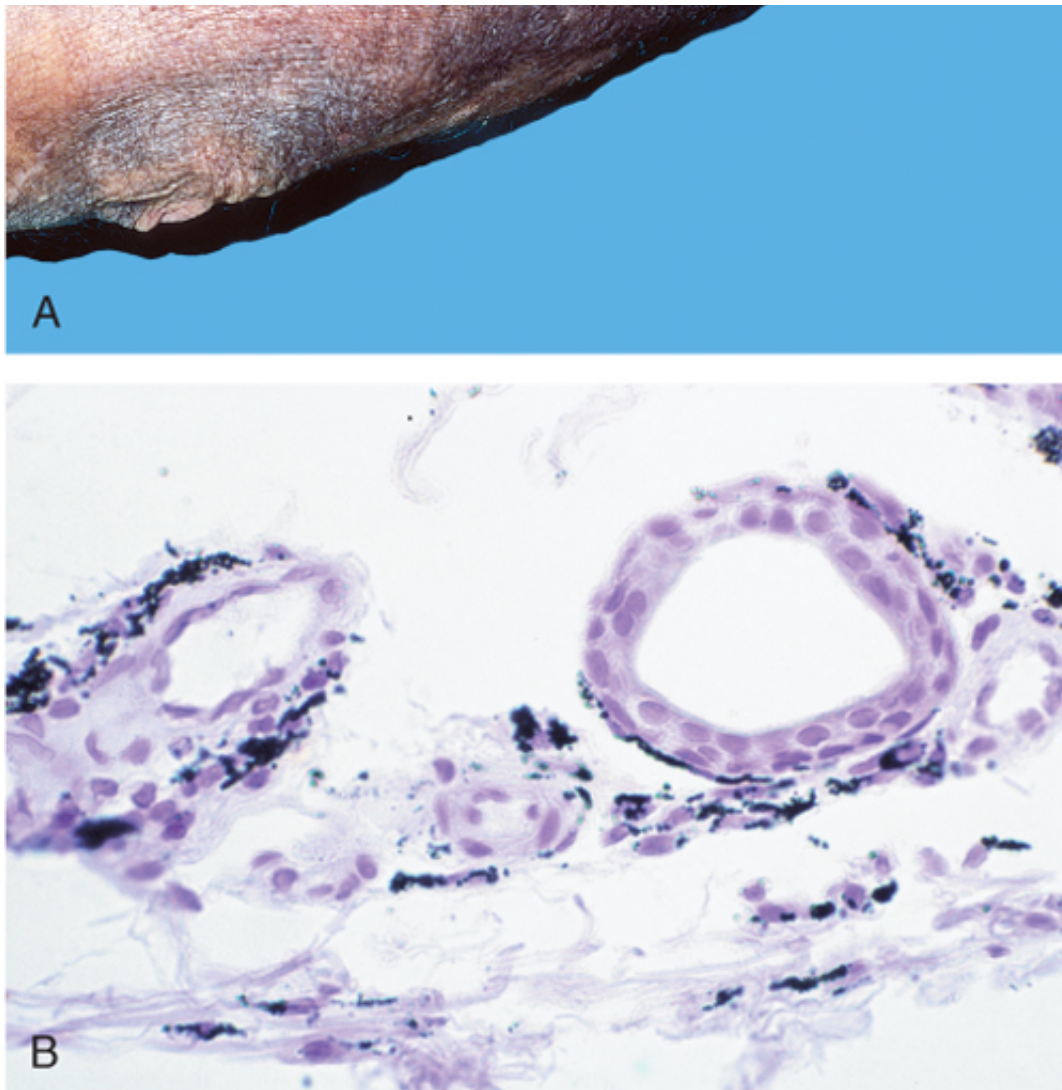
Estrogen therapy, once used primarily for distressing menopausal symptoms (e.g., hot flashes), has been widely used in postmenopausal women, with or without added progestins, to prevent or slow the progression of osteoporosis ([Chapter 21](#)) and to reduce the likelihood of myocardial infarction. Such therapy is referred to as *hormone replacement therapy* (HRT). Given the fact that endogenous hyperestrinism increases the risk of developing ovarian carcinoma and, probably, breast carcinoma, there is understandable concern about the use of HRT. The main focus of controversy is the potential benefit of HRT as protection against ischemic myocardial disease. *Recent data has confirmed the adverse effects of HRT on endometrial and breast cancers but does not support the view that HRT offers protection against ischemic heart disease.* Here is a summary of the main adverse effects of HRT.

Results from randomized control trials show that *HRT increases the risk of ovarian cancer*. Unopposed estrogen therapy increases the risk of *endometrial carcinoma* three- to sixfold after 5 years of use and more than 10-fold after 10 years, but the risk is drastically reduced or eliminated when progestins are added to the therapeutic regimen. Therefore, estrogen in combination with a progestin is most commonly in use today for postmenopausal women. HRT causes a small increase in the risk of *breast cancers*. The risk of breast cancer is *not* eliminated by the combination of estrogen and progestins; quite the contrary, the combination therapy *increases* the risk over that for women taking estrogen alone. HRT increases risk of *venous thromboembolism*, including deep vein thrombosis, pulmonary embolism, and stroke, by about twofold. The increase is more pronounced during the first 2 years of treatment and in women who have other risk factors such as immobilization or factor V or prothrombin mutations. Estrogens and progestins increase blood levels of high-density lipoprotein and decrease levels of low-density lipoprotein. It was thought that these effects would be beneficial in protecting against atherosclerosis and ischemic heart disease. Indeed, several epidemiologic studies had suggested in the past that HRT beginning at or near the onset of menopause protected against ischemic heart disease. However, recently published large and well-controlled studies did not demonstrate a protective effect of HRT on the risk of myocardial infarction.

### Oral Contraceptives







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 Figure 8-10 Adverse reaction to minocycline, a long-acting tetracycline derivative. **A**, Diffuse blue-gray pigmentation of the forearm, secondary to minocycline administration. **B**, Deposition of drug metabolite/iron/melanin pigment particles in the dermis. (Courtesy of Dr. Zsolt Argenyi, Department of Pathology, University of Washington, Seattle, Washington.)

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Although OCs have been in use for over 30 years, and despite innumerable analyses of their risks and benefits, disagreement continues about their safety and adverse effects. They nearly always contain a synthetic **estradiol** and a variable amount of a progestin (combined OCs), but a few preparations contain only progestins. Currently prescribed OCs contain a smaller amount of estrogens ( $<50 \mu\text{g/day}$ ) and are clearly associated with fewer side effects than were earlier formulations. Hence, the results of epidemiologic studies must be interpreted in the context of the dosage. Nevertheless, there is reasonable evidence to support the following conclusions:

**Breast carcinoma.** Despite the disagreements, the prevailing opinion is that OCs do not cause an increase in breast cancer risk. **Endometrial cancer and ovarian cancers.** OCs have a protective effect against these tumors. **Cervical cancer.** OCs may increase risk of cervical carcinomas in women infected with human papilloma virus, although it is unclear whether the increased risk results from sexual activity. **Thromboembolism.** Most

studies indicate that OCs, including the newer low-dose (<50 µg of estrogen) preparations, are clearly associated with a three- to sixfold increased risk of venous thrombosis and pulmonary thromboembolism because of increased hepatic synthesis of coagulation factors. This risk may be even higher with newer "third-generation" OCs that contain synthetic progestins, particularly in women who are carriers of the factor V Leiden mutation. The increased thrombotic risk from these agents seems to be a consequence of the generation of an acute-phase response, with increases in C-reactive protein and plasma viscosity. *Cardiovascular disease.* There is considerable uncertainty about the risk of atherosclerosis and myocardial infarction in users of OCs. It seems that OCs do not increase the risk of coronary artery disease in women younger than 30 years or in older women who are nonsmokers, but the risk does increase by about twofold in women older than 35 years who smoke. *Hepatic adenoma.* There is a well-defined association between the use of OCs and this rare benign hepatic tumor, especially in older women who have used OCs for prolonged periods. The tumor appears as a large, solitary, and well-encapsulated mass.

Obviously, the pros and cons of OCs must be viewed in the context of their wide applicability and acceptance as a form of contraception that protects against unwanted pregnancies.

### **Acetaminophen**

At therapeutic doses, acetaminophen<sup>®</sup>, a widely used nonprescription analgesic and antipyretic, is mostly conjugated in the liver with glucuronide or sulfate. About 5% or less is metabolized to NAPQI (*N*-acetyl-*p*-benzoquinoneimine) through the P-450 system. However, when taken in very large doses, NAPQI accumulates, leading to hepatic necrosis localized in the centrilobular areas of the hepatic lobules. The mechanisms of injury produced by NAPQI include (1) covalent binding to hepatic proteins and (2) depletion of glutathione (GSH). The depletion of GSH makes the hepatocytes more susceptible to cell death caused by reactive oxygen species. The window between the usual therapeutic dose (0.5 gm) and the toxic dose (15-25 gm) is large, and the drug is ordinarily very safe. Nevertheless accidental overdosage occurs in children, and suicide attempts using acetaminophen<sup>®</sup> are not uncommon in adults, particularly in the United Kingdom. Toxicity begins with nausea, vomiting, diarrhea, and sometimes shock, followed in a few days by jaundice. Overdoses of acetaminophen<sup>®</sup> can be treated at its early stages by administration of N-acetylcysteine, which restores GSH. With serious overdose, liver failure ensues. There is centrilobular necrosis that may extend to entire lobules, requiring liver transplantation for survival. Some patients show evidence of concurrent renal damage.

### **Aspirin (Acetylsalicylic Acid)**

Overdose may result from accidental ingestion of a large number of 325mg tablets by young children; in adults, overdose is frequently suicidal. The major untoward consequences are metabolic, with few morphologic changes. At first, respiratory alkalosis develops, followed by a metabolic acidosis that often proves fatal before anatomic changes can appear. Ingestion of as little as 2 to 4 gm by children or 10 to 30 gm by adults may be fatal, but survival has been reported after doses five times larger.

Chronic aspirin<sup>®</sup> toxicity (salicylism) may develop in persons who take 3 gm or more daily (the dose required to treat chronic inflammatory conditions). Chronic salicylism is manifested by headache, dizziness, ringing in the ears (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, and diarrhea. The CNS changes may progress to convulsions and coma. The morphologic consequences of chronic salicylism are varied. Most often, there is an acute erosive gastritis (Chapter 15), which may produce overt or covert GI bleeding and lead to gastric ulceration. A bleeding tendency may appear concurrently with chronic toxicity, because aspirin<sup>®</sup> acetylates platelet cyclooxygenase and blocks the ability to make thromboxane A<sub>2</sub>, an activator of platelet aggregation. Petechial hemorrhages may appear in

the skin and internal viscera, and bleeding from gastric ulcerations may be exaggerated.

Proprietary analgesic mixtures of [aspirin<sup>Rx</sup>](#) and phenacetin or its active metabolite, [acetaminophen<sup>Rx</sup>](#), when taken over several years, can cause tubulointerstitial nephritis with renal papillary necrosis, referred to as *analgesic nephropathy* ([Chapter 14](#)).

### Injury by Nontherapeutic Toxic Agents (Drug Abuse)

Drug abuse generally involves the use of mind-altering substances, beyond therapeutic or social norms. Drug addiction and overdose are serious public health problems. Common drugs of abuse are listed in [Table 8-6](#). Here we consider cocaine, heroin, and marijuana, and briefly mention a few other drugs.

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**Table 8-6. Common Drugs of Abuse**

Class	Molecular Target	Example
Opioid narcotics	Mu opioid receptor (agonist)	Heroin, hydromorphone (Dilaudid)
		Oxycodone (Percodan, Percocet, Oxycontin)
		Methadone (Dolophine)
		Meperidine (Demerol)
Sedative-hypnotics	GABA <sub>A</sub> receptor (agonist)	Barbiturates
		Ethanol
		Methaqualone (Quaalude)
		Glutethimide (Doriden)
Psychomotor stimulants	Dopamine transporter (antagonist)	<a href="#">Ethchlorvynol<sup>Rx</sup></a> (Placidyl)
		Cocaine
		Amphetamine
		3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
Phencyclidine-like drugs	NMDA glutamate receptor channel (antagonist)	Phencyclidine (PCP, angel dust)
		Ketamine
Cannabinoids	CBI cannabinoid receptors (agonist)	Marijuana
		Hashish
<a href="#">Nicotine<sup>Rx</sup></a>	<a href="#">Nicotine<sup>Rx</sup></a> acetylcholine receptor (agonist)	Tobacco products
Hallucinogens	Serotonin 5-HT <sub>2</sub> receptors (agonist)	Lysergic acid diethylamide (LSD)
		Mescaline
		Psilocybin

Data from Hyman SE: A 28-year-old man addicted to cocaine. JAMA 286:2586, 2001. GABA,  $\gamma$ -aminobutyric acid; 5-HT<sub>2</sub>, 5-hydroxytryptamine; NMDA, N-methyl D-aspartate.

### Cocaine

There has been a major escalation in the use of cocaine, along with its derivative "crack"; currently, there are an estimated 2 to 6 million cocaine users in the United States. Approximately 1.1% of middle-school and 2.3% of high-school students reported the use of cocaine in the month preceding a survey. Extracted from the leaves of the coca plant, cocaine is usually prepared as a water-soluble powder, [cocaine hydrochloride<sup>Rx</sup>](#), but when sold on the

street it is liberally diluted with talcum powder, lactose, or other look-alikes. Crystallization of the pure alkaloid from **cocaine hydrochloride<sup>®</sup>** yields nuggets of crack (so called because of the cracking or popping sound it makes when heated). The pharmacologic actions of cocaine and crack are identical, but crack is far more potent. Both forms of the drug are absorbed from all sites and so can be snorted, smoked after mixing with tobacco, ingested, or injected subcutaneously or intravenously.

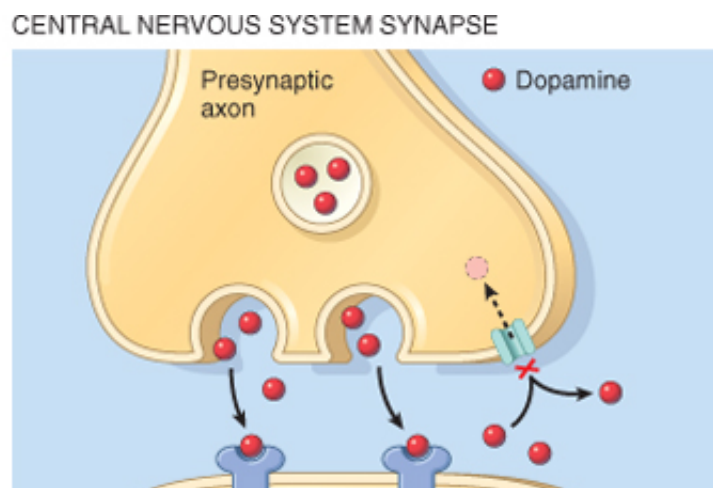
Cocaine produces an intense euphoria and stimulation, making it one of the most addictive of all drugs. Experimental animals will press a lever more than 1000 times and forgo food and drink to obtain the drug. In the cocaine user, although physical dependence seems not to occur, the psychological withdrawal is profound and can be extremely difficult to treat. Intense cravings are particularly severe in the first several months after abstinence and can recur for years. Acute overdose produces seizures, cardiac arrhythmias, and respiratory arrest. The following are the important manifestations of cocaine toxicity.

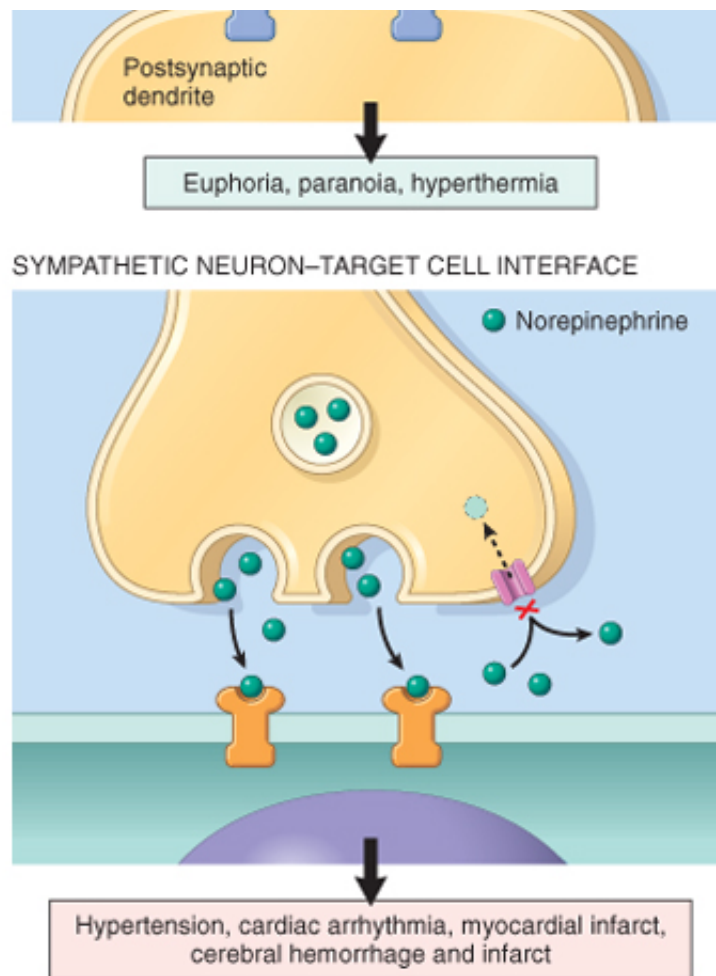
**Cardiovascular effects.** The most serious physical effects of cocaine relate to its acute action on the cardiovascular system, where it behaves as a sympathomimetic agent (Fig. 8-11). It facilitates neurotransmission both in the CNS, where it blocks the reuptake of dopamine, and at adrenergic nerve endings, where it blocks the reuptake of both **epinephrine<sup>®</sup>** and norepinephrine while stimulating the presynaptic release of norepinephrine. The net effect is the accumulation of these two neurotransmitters in synapses, resulting in excess stimulation, manifested by *tachycardia*, *hypertension*, and *peripheral vasoconstriction*. Cocaine also induces *myocardial ischemia*, the basis for which is multifactorial. It causes *coronary artery vasoconstriction* and promotes thrombus formation by facilitating platelet aggregation. Cigarette smoking potentiates cocaine-induced coronary vasospasm. Thus, the dual effect of cocaine, causing increased myocardial oxygen demand by its sympathomimetic action and, at the same time, reducing coronary blood flow, sets the stage for myocardial ischemia that may lead to myocardial infarction. Cocaine can also precipitate *lethal arrhythmias* by enhanced sympathetic activity as well as by disrupting normal ion ( $K^+$ ,  $Ca^{2+}$ ,  $Na^+$ ) transport in the myocardium. These toxic effects are not necessarily dose related, and a fatal event may occur in a first-time user with what is a typical mood-altering dose.

**CNS effects.** The most common CNS findings are hyperpyrexia (thought to be caused by aberrations of the dopaminergic pathways that control body temperature) and seizures.

**Effects on the fetus.** In pregnant women, cocaine may cause decreased blood flow to the placenta, resulting in fetal hypoxia and spontaneous abortion. Neurologic development may be impaired in the fetus of pregnant women who are chronic drug users.

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 Figure 8-11 The effect of cocaine on neurotransmission. The drug inhibits reuptake of the neurotransmitters dopamine and norepinephrine in the central and peripheral nervous systems.

**Chronic cocaine use.** Chronic use may cause (1) perforation of the nasal septum in snorters, (2) decrease in lung diffusing capacity in those who inhale the smoke, and (3) the development of dilated cardiomyopathy.

### Heroin

Heroin is an addictive opioid derived from the poppy plant and is closely related to morphine. Its effects are even more harmful than those of cocaine. As sold on the street, it is cut (diluted) with an agent (often talc or quinine); thus, the size of the dose is not only variable but also usually unknown to the buyer. The heroin, along with any contaminating substances, is usually self-administered intravenously or subcutaneously. Effects are varied and include euphoria, hallucinations, somnolence, and sedation. Heroin has a wide range of adverse physical effects related to (1) the pharmacologic action of the agent, (2) reactions to the cutting agents or contaminants, (3) hypersensitivity reactions to the drug or its adulterants (quinine itself has neurologic, renal, and auditory toxicity), and (4) diseases contracted incident to the use of the needle. Some of the most important adverse effects of heroin are the following:

**Sudden death.** Sudden death, usually related to overdose, is an ever-present risk because drug purity is generally unknown and may range from 2% to 90%. The yearly mortality in the United States is estimated to be between 1% and 3%. Sudden death can also occur if tolerance for the drug, built up over time, is lost (as during a period of



can also occur if tolerance for the drug, built up over time, is lost (as during a period of incarceration). The mechanisms of death include profound respiratory depression, arrhythmia and cardiac arrest, and severe pulmonary edema. *Pulmonary problems.* Pulmonary complications include moderate to severe edema, septic embolism, lung abscess, opportunistic infections, and foreign body granulomas from talc and other adulterants. Although granulomas occur principally in the lung, they are sometimes found in the mononuclear phagocyte system, particularly in the spleen, liver, and lymph nodes that drain the upper extremities. Examination under polarized light often highlights trapped talc crystals, sometimes enclosed within foreign body giant cells. *Infections.* Infectious complications are common. The four sites most commonly affected are the skin and subcutaneous tissue, heart valves, liver, and lungs. In a series of addicted patients admitted to the hospital, more than 10% had endocarditis, which often takes a distinctive form involving right-sided heart valves, particularly the tricuspid. Most cases are caused by *Staphylococcus aureus*, but fungi and a multitude of other organisms have also been implicated. Viral hepatitis is the most common infection among addicted persons and is acquired by the sharing of dirty needles. In the United States, this practice has also led to a very high incidence of acquired immunodeficiency syndrome in intravenous drug abusers. *Skin.* Cutaneous lesions are probably the most frequent telltale sign of heroin addiction. Acute changes include abscesses, cellulitis, and ulcerations due to subcutaneous injections. Scarring at injection sites, hyperpigmentation over commonly used veins, and thrombosed veins are the usual sequelae of repeated intravenous inoculations. *Renal problems.* Kidney disease is a relatively common hazard. The two forms most frequently encountered are amyloidosis (generally secondary to skin infections) and focal glomerulosclerosis; both induce heavy proteinuria and the nephrotic syndrome.

## **Marijuana**

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Marijuana or "pot" is the most widely used illegal drug. It is made from the leaves of the *Cannabis sativa* plant, which contain the psychoactive substance  $\Delta^9$ -tetrahydrocannabinol (THC). When it is smoked about 5% to 10% is absorbed. Despite numerous studies, the central question of whether the drug has persistent adverse physical and functional effects remains unresolved. Some of the untoward anecdotal effects may be allergic or idiosyncratic reactions or may possibly be related to contaminants in the preparations rather than to marijuana's pharmacologic effects. On the other hand, two beneficial effects of THC are its capacity to decrease intraocular pressure in glaucoma and to combat intractable nausea secondary to cancer chemotherapy.

The functional and organic CNS consequences of marijuana have received great scrutiny. Clearly, its use distorts sensory perception and impairs motor coordination, but these acute effects generally clear in 4 to 5 hours. With continued use these changes may progress to cognitive and psychomotor impairments, such as inability to judge time, speed, and distance. Among adolescents, such changes often lead to automobile accidents. Marijuana increases the heart rate and sometimes blood pressure, and it may cause angina in a person with coronary artery disease.

The lungs are affected by chronic marijuana smoking; laryngitis, pharyngitis, bronchitis, cough and hoarseness, and asthma-like symptoms have all been described, along with mild but significant airway obstruction. Smoking a marijuana cigarette, compared with a tobacco cigarette, is associated with a threefold increase in the amount of tar inhaled and retained in the lungs. Presumably, the larger puff volume, deeper inhalation, and longer breath holding are responsible.

## **Other Illicit Drugs**

The variety of drugs that have been tried by those seeking "new experiences" (highs, lows, "out-of-body experiences") defies belief. They include various stimulants, depressants, analgesics, and hallucinogens. Among these are PCP (phenylcyclidine, an anesthetic agent), LSD (lysergic acid diethylamide, the most potent hallucinogen known), "ecstasy" (MDMA, 3,4-methylenedioxymethamphetamine), oxycodone (an analgesic), and ketamine (an anesthetic agent used in animal surgery). Because they are used haphazardly and in various combinations, not much is known about their long-time deleterious effects, but LSD and ecstasy can cause serious health effects. Regarding their acute effects, this much is clear: they cause bizarre and often aggressive behavior that leads to violence, or depressive moods that may verge on suicide. Consumed in combination with alcohol, they are deadly agents of driving accidents.

## SUMMARY

**Drug Injury** Drug injury may be caused by therapeutic drugs (adverse drug reactions) or non-therapeutic agents (drug abuse). Antineoplastic agents, long-acting tetracyclines and other antibiotics, hormone replacement therapy (HRT) and oral contraceptives (OC), [acetaminophen<sup>®</sup>](#), and [aspirin<sup>®</sup>](#) are the drugs most frequently involved. HRT increases the risk of ovarian and breast cancers, and thromboembolism, but does not appear to protect against ischemic heart disease. OCs have a protective effect on endometrial and ovarian cancers, but increase the risk of thromboembolism and hepatic adenomas. Overdose of [acetaminophen<sup>®</sup>](#) may cause centrilobular liver necrosis leading to liver failure. Early toxicity may be prevented by agents that restore GSH levels. [Aspirin<sup>®</sup>](#) blocks the production of thromboxane A<sub>2</sub> and may produce gastric ulceration and bleeding. The common drugs of abuse include psychomotor stimulants (cocaine, amphetamine, ecstasy), opioid narcotics (heroin, methadone, oxycodone), hallucinogens (LSD, mescaline), cannabinoids (marijuana, hashish) and sedative hypnotics (barbiturates, ethanol).



## INJURY BY PHYSICAL AGENTS

Injury induced by physical agents is divided into the following categories: mechanical trauma, thermal injury, and injury produced by ionizing radiation. Each type is considered separately.

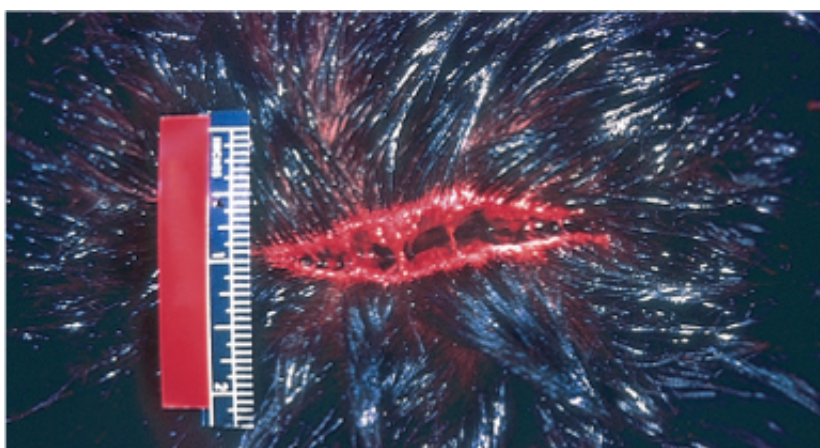
### Mechanical Trauma

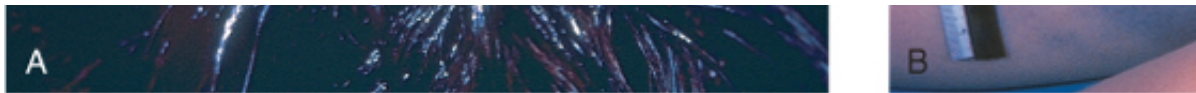
Mechanical forces may inflict a variety of forms of damage. The type of injury depends on the shape of the object, the energy discharged at impact, and the tissues or organs that bear the impact. Bone and head injuries are discussed elsewhere ([Chapter 23](#)). All soft tissues react similarly to mechanical forces, and the pattern of injury depends on the type of force: abrasions, contusions, lacerations, incised wounds, and puncture wounds ([Fig. 8-12](#)).

### Morphology

An **abrasion** is a wound produced by scraping or rubbing, resulting in removal of the epidermal layer. A **contusion**, or bruise, is a wound produced by a blunt object and is characterized by damage to blood vessels and extravasation of blood. A **laceration** is a tear or disruptive stretching of tissue caused by the application of force. In contrast to an incision, most lacerations have intact bridging blood vessels and jagged edges. An **incised wound** is one inflicted by a sharp instrument. The bridging blood vessels are intact. A **penetrating wound** is caused by a long, narrow instrument and is termed penetrating when the instrument enters the tissue and perforating when it traverses a tissue to also create an exit wound. Gunshot wounds are a form of penetrating wound that demonstrate distinctive features important to the forensic pathologist. For example, a wound from a bullet fired at close range leaves powder burns, whereas a wound fired 4 or 5 feet away does not.

One of the most common causes of mechanical injury is **vehicular accident**. Injuries result from (1) hitting a part of the interior of the vehicle or being hit by objects that become airborne during the crash, such as engine parts; (2) being thrown from the vehicle; or (3) being trapped in a burning vehicle. The pattern of injury relates to whether one or all three of these mechanisms are operative. For example, in a head-on collision, a common pattern of injury sustained by a person wearing a seat belt includes trauma to the head (windshield impact), chest (steering wheel impact), and knees (dashboard impact). Under these conditions, common chest injuries include heart contusions, aortic lacerations, and (less commonly) lacerations of the spleen. For an automobile injury victim, it is essential to remember that internal wounds often occur without external evidence of abrasions, contusions, and lacerations. Indeed, in many cases, external evidence of injury is completely absent.





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 Figure 8-12 **A**, Laceration of the scalp: the bridging strands of fibrous tissues are evident. **B**, Contusion resulting in hemorrhage of subcutaneous vessels, producing extensive discoloration. (From the teaching collection of the I Southwestern Medical School, Dallas, Texas.)

## Thermal Injury

Both excess heat and excess cold are important causes of injury. Burns are all too common and a hyperthermia and hypothermia follows.

### Thermal Burns

In the United States, burns cause 5000 deaths per year and result in the hospitalization of more than 1 million victims are children, who are often scalded by hot liquids. Fortunately, since the 1970s marked decreases in mortality rates and the length of hospitalizations. These improvements have been achieved by a better understanding of massive burns and discoveries of better ways to prevent wound infection and facilitate the healing process.

The clinical significance of burns depends on the following important variables:

- Depth of the burn
- Percentage of body surface involved
- Possible presence of internal injuries
- Availability of medical supplies and equipment
- Timing and promptness and efficacy of therapy, especially fluid and electrolyte management and antibiotic therapy
- Prevention of infections

A *full-thickness* burn involves total destruction of the epidermis and dermis, with loss of the dermal papillae and dermal cells for epithelial regeneration. Both third- and fourth-degree burns are in this category. In *partial-thickness* burns, portions of the dermal appendages are spared. Partial-thickness burns include first-degree burns (involving only the epidermis) and second-degree burns (involving both epidermis and superficial dermis).

### Morphology

Grossly, full-thickness burns are white or charred, dry, and anesthetic (because of destruction of nerve endings). Partial-thickness burns are pink or mottled with redness. Histologically, devitalized tissue reveals coagulative necrosis, adjacent to vital tissue, which accumulates inflammatory cells and marked exudation.

Despite continuous improvement in therapy, any burn exceeding 50% of the total body surface, with associated hypovolemia, is potentially fatal. With burns of more than 20% of the body surface, there is a rapid shift of body fluids from the intravascular space to the interstitial space, both at the burn site and systemically, which can result in hypovolemic shock (Chapter 4). Because of the high permeability of the burn site, interstitial tissue, generalized edema, including pulmonary edema, may become severe.

Another important consideration in patients with burns is the degree of injury to the airways and lungs. Persons trapped in burning buildings and may result from the direct effect of heat on the mouth, nose, and throat, or from the inhalation of heated air and gases in the smoke. Water-soluble gases, such as chlorine, sulfur dioxide, and ammonia, can form acids or alkalis, particularly in the upper airways, and so produce inflammation and swelling, leading to airway obstruction. Lipid-soluble gases, such as nitrous oxide and products of burning plastics, are more likely to produce pulmonary damage, producing pneumonitis. Unlike shock, which develops within hours, pulmonary manifestations may develop later.

Organ system failure resulting from burn sepsis continues to be the leading cause of death in burn patients. The rapid growth of microorganisms; the serum and debris provide nutrients, and the burn injury compromises the host's inflammatory responses. The most common offender is the opportunist *Pseudomonas aeruginosa*, a common hospital-acquired bacteria, such as *S. aureus*, and fungi, particularly *Candida* species, and humoral defenses against infections are compromised, and both lymphocyte and phagocyte function are impaired. The spread and release of toxic substances such as endotoxin from the local site have dire consequences.

renal failure and/or the acute respiratory distress syndrome (ARDS) ([Chapter 13](#)) are the most common.

Another very important pathophysiologic effect of burns is the development of a hypermetabolic state with an increased need for nutritional support. It is estimated that when more than 40% of the body surface is burned, the metabolic rate may approach twice normal.

### **Hyperthermia**

Prolonged exposure to elevated ambient temperatures can result in heat cramps, heat exhaustion, and heat stroke.

*Heat cramps* result from loss of electrolytes via sweating. Cramping of voluntary muscles, especially during exercise, is the hallmark. Heat-dissipating mechanisms are able to maintain normal core body temperature. Heat exhaustion is probably the most common hyperthermic syndrome. Its onset is sudden, with prostration and hypotension. The cardiovascular system compensates for hypovolemia, secondary to water depletion. After a brief period, equilibrium is spontaneously re-established. *Heat stroke* is associated with high ambient temperatures. Thermoregulatory mechanisms fail, sweating ceases, and core body temperature rises. It has been recorded in some terminal cases. Clinically, a rectal temperature of 106°F or higher is associated with a mortality rate for such patients that exceeds 50%. The underlying mechanism is marked generalized peripheral pooling of blood and a decreased effective circulating blood volume. Necrosis of tissues may occur. Arrhythmias, disseminated intravascular coagulation, and other systemic effects are seen. It is most common in individuals undergoing intense physical stress (including young athletes and military recruits), and per se, they are prime candidates for heat stroke.

### **Hypothermia**

Prolonged exposure to low ambient temperature leads to hypothermia, a condition seen all too frequently in outdoor workers, hikers, and soldiers. It is caused by exposure to cold, wet clothing, and dilation of superficial blood vessels occurring as a result of the ingested cold. At about 90°F, loss of consciousness occurs, followed by bradycardia and atrial fibrillation.

### **Local Reactions**

Chilling or freezing of cells and tissues causes injury by two mechanisms:

*Direct effects* are probably mediated by physical disruptions within cells and high salt concentrations within intra- and extracellular water.

*Indirect effects* are the result of circulatory changes. Depending on the rate at which the temperature falls, slowly developing chilling may induce vasoconstriction and increased permeability, leading to edema. "Frostbite" is a common result. Atrophy and fibrosis may follow. Alternatively, with sudden sharp drops in temperature that cause increased viscosity of the blood in the local area may cause ischemic injury and degenerative changes. In this situation, only after the temperature begins to return to normal do the vascular injury and edema become evident. However, during the period of ischemia hypoxic changes and infarction of the affected tissues (e.g., fingers or feet) may occur.

### **Electrical Injury**

Electrical injuries, which may result in death, can arise from low-voltage currents (i.e., in the home from household wiring), or from high-power lines or lightning. Injuries are of two types: (1) burns and (2) ventricular fibrillation. The type of injury and the severity depend on the voltage, the amperage, and the path of the electric current within the body.

Voltage in the household and workplace (120 or 220 V) is high enough that with low resistance at the point of contact (e.g., wet skin), sufficient current can pass through the body to cause serious injury, including ventricular fibrillation. If the current is high enough, it generates enough heat to produce burns at the site of entry and exit as well as in internal tissues. Alternating current, the type available in most homes, is that it induces tetanic muscle spasm, so that irreversible clenching is likely to occur, prolonging the period of current flow. This results in a great deal of tissue damage, including electrical burns and, in some cases, spasm of the chest wall muscles, producing death from asphyxiation.



voltage sources cause similar damage; however, because of the large current flows generated, the effects on the central nervous system, particularly on the centers of medullary centers and extensive burns. Lightning is a classic cause of high-voltage electrical injury.

Before leaving the subject of electrical injury, we should briefly mention the health risks of exposure to electromagnetic fields (EMFs), particularly those generated by transmission lines. Earlier studies linked exposure to EMFs to an increased risk of leukemia, among electrical workers who worked on high-power lines and among children living near high-voltage power lines. *Further analyses failed to confirm these findings.* EMF and microwave radiation, when sufficiently intense, can cause burns of the skin and subjacent connective tissue, and both forms of radiation can interfere with cardiac pacemakers.

### **Injury Produced by Ionizing Radiation**

Radiation is energy that travels in the form of waves or high-speed particles. Radiation has a wide electromagnetic spectrum; it can be divided into nonionizing and ionizing radiation. The energy of visible light (UV) and infrared light, microwaves, and sound waves, can move atoms in a molecule or cause them to vibrate, but cannot displace bound electrons from atoms. By contrast, *ionizing radiation has sufficient energy to remove electrons from atoms.* Ionizing radiation includes (1) *x-rays and γ rays*, which are electromagnetic waves of very high frequencies, and (2) *high-energy particles* (alpha particles, which consist of two protons and two neutrons), and *beta particles*, which are essentially electrons. About 18% of the ionizing radiation received by the US population is human made, originating for the most part in medical devices and procedures.

Ionizing radiation is indispensable in medical practice, but it is a two-edged sword. It is used in the diagnosis of disease, in cancer therapy, and as therapeutic or diagnostic radioisotopes. However, it is also *mutagenic, carcinogenic, and teratogenic*. The units used to express exposure, absorption, and dose of ionizing radiation are:

**Roentgen (R)**, introduced in 1928, was the first unit of radiation measurement. It measures the exposure of air to x- or γ radiation. It represents the quantity of electrical charge produced in air by X- or γ radiation (1 R produces 2.58 × 10<sup>7</sup> ion pairs per cubic centimeter of air). **Gray (Gy)** is a unit that expresses the energy absorbed by a target. 1 Gy is equivalent to an absorption of 10<sup>4</sup> ergs/gm of tissue. The centigray (cGy), which is the absorption of 100 ergs/gm, is equivalent to the exposure of tissue to 100 R. **Sievert (Sv)** is a unit of equivalent dose that takes into account the biological effects of radiation. For the same absorbed dose, various types of radiation differ in their biological effects. The equivalent dose equalizes this variation and provides a uniform measuring unit. *The equivalent dose is calculated as follows: Equivalent dose (Sv) = absorbed dose (expressed in Grays) × the relative biological effect (RBE).* The RBE depends on the type of radiation, the type and volume of tissue exposed to radiation, the dose rate, and other biologic factors (discussed below). For instance, if equivalent amounts of energy enter the body, alpha particles would cause heavy damage in a restricted area, whereas γ rays would disperse the energy and produce considerably less damage per unit of tissue. The effective dose of x-rays and other imaging and nuclear medicine procedures are commonly expressed in millisieverts (mSv). The dosage of a single-film chest x-ray is approximately 0.01 mSv, while that of a CT scan of the abdomen is approximately 10 mSv. The becquerel (Bq) represents the disintegrations per second of a spontaneously disintegrating radionuclide (1 Ci = 3.7 × 10<sup>10</sup> Bq).

In addition to the physical properties of the radiation, its biologic effects depend heavily on the following factors:

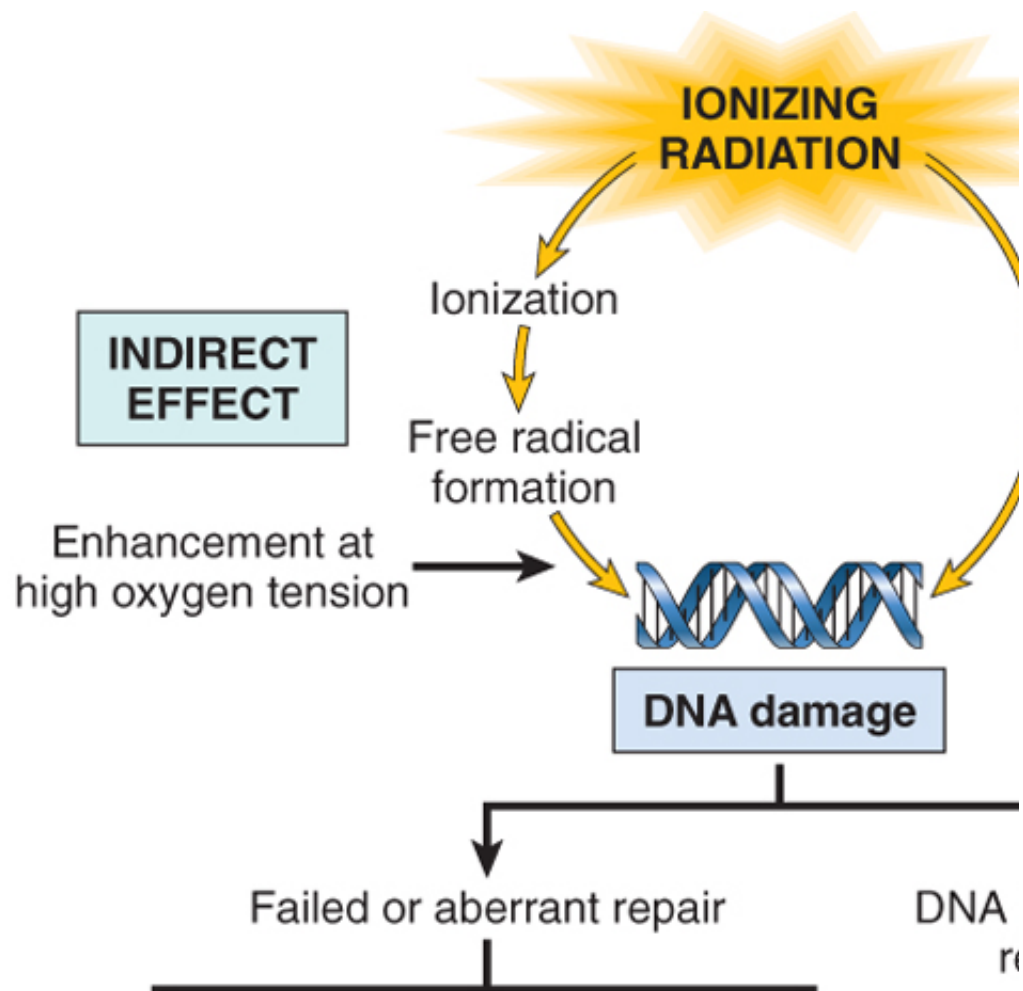
**Sensitivity of proliferating tissues.** Because ionizing radiation damages DNA, rapidly dividing cells are particularly sensitive. Except at extremely high doses that impair DNA transcription, DNA damage is repaired in nondividing cells; however, during mitosis cells that have incurred irreparable DNA damage undergo apoptosis. Understandably, therefore, *tissues with a high rate of cell division, such as bone marrow, lymphoid tissue, and the mucosa of the GI tract, are extremely vulnerable to radiation injury.* Tissues with nondividing cells, such as brain and myocardium, do not suffer as much damage, although high-dose radiation can affect transcription of vital molecules. **Vascular damage.** Because the effects of radiation are complex, damage to endothelial cells, which are moderately sensitive to radiation, can lead to occlusion of blood vessels, leading to impaired healing, fibrosis, and chronic ischemic atrophy of the tissue. **Rate of delivery.** The rate of delivery significantly affects the biological effect of radiation. A high dose rate causes more damage than a low dose rate.

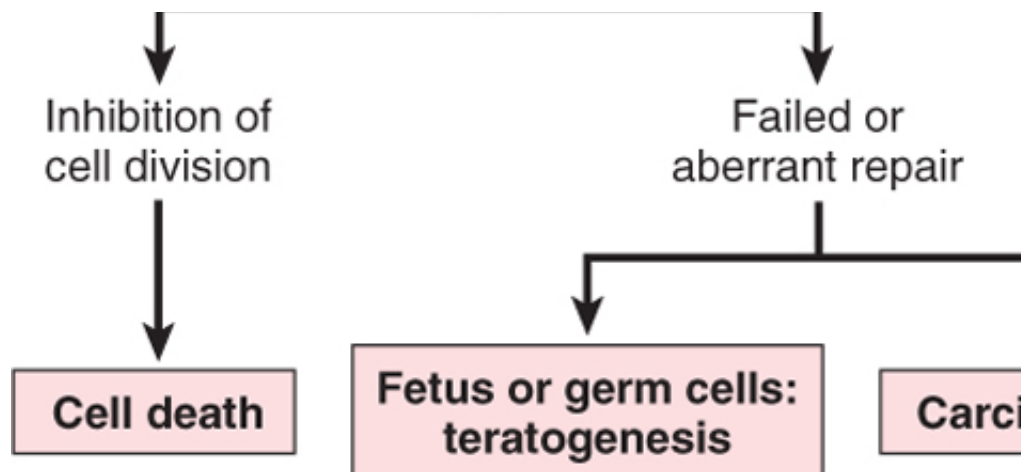
Although the effect of radiant energy is cumulative, delivery in divided doses may allow cell intervals. Thus, fractional doses of radiant energy have a cumulative effect only to the extent incomplete. Radiotherapy of tumors exploits the capability of normal cells to self-repair and avoiding much cumulative radiation damage. *Hypoxia*. Ionizing radiation may directly damage DNA (often it does so indirectly, by producing free radicals from the radiolysis of water or interaction with oxygen (the free radical theory)). Therefore, hypoxic tissues are relatively resistant to radiation injury. This is particularly true for hypoxic neoplasms. The center of rapidly growing tumors may be poorly vascularized and therefore less effective. *Field size*. The size of the field exposed to radiation has a great influence on the outcome. Relatively high doses of radiation when they are delivered to small, carefully shielded fields, larger fields may be lethal.

### DNA Damage and Carcinogenesis

Because its most important target is DNA, ionizing radiation kills dividing cells, and, as a consequence, it can have delayed effects that are manifested years or decades later. Ionizing radiation causes damage in DNA, including base damage, single- and double-strand breaks, and cross-links between DNA strands. Simple defects may be reparable by various enzyme repair systems contained in mammalian cells. These repair systems are linked to cell cycle regulation through the activity of genes such as *ATM* that initiate signal transduction pathways which can transiently slow down the cell cycle to allow for DNA repair or trigger apoptosis of cells. If strand breaks may persist without repair, or the repair of the lesion may be defective, creating malfunctioning (for instance, because of a mutation in *p53*), cells with abnormal and unstable genomes that can eventually form tumors.

### Fibrosis





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 Figure 8-13 Effects of ionizing radiation on DNA and their consequences. The effects on DNA can be direct or, indirectly, through the formation of free radicals.

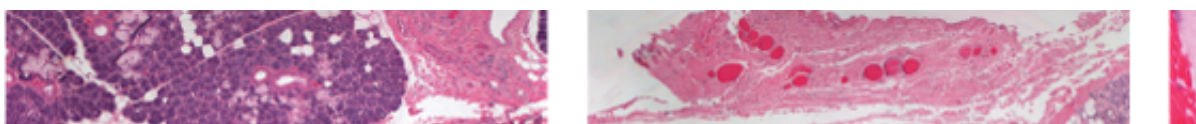
A common consequence of radiation therapy for cancer is the development of fibrosis in the tissues (Fig. 8-14). Fibrosis may occur weeks or months after irradiation, leading to the replacement of dead parts of the tissue by the formation of scars and adhesions (see Chapter 3). As already mentioned, ionizing radiation causes tissue ischemia. Vascular damage, the killing of tissue stem cells by ionizing radiation, and the release of cytokines promote an inflammatory reaction and fibroblast activation are the main contributors to the development of fibrosis.

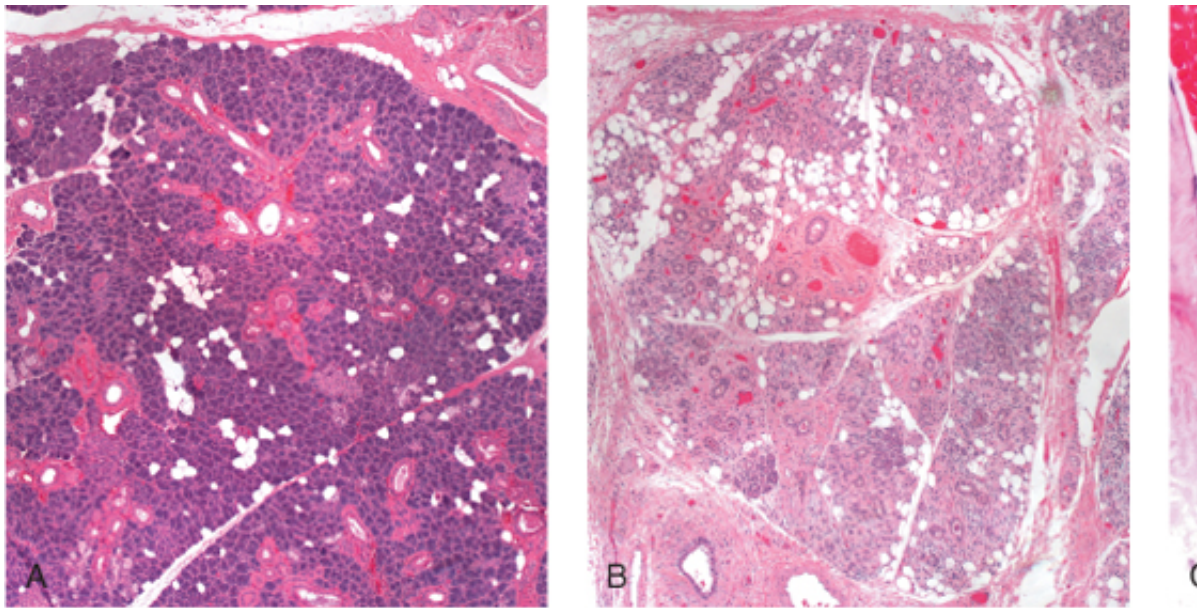
### Morphology

Cells surviving radiant energy damage show a wide range of structural changes including nuclear changes such as deletions, breaks, translocations, and fragmentation. The mitotic spindle often becomes abnormal. Polyploidy and aneuploidy may be encountered. **Nuclear swelling** and condensation of chromatin may appear; sometimes the nuclear membrane breaks. **Apoptosis** may occur. Abnormal nuclear morphology may be produced. Giant cells with pleomorphic nuclei may appear and persist for years after exposure. At extremely high doses, nuclear pyknosis or lysis appears quickly as a marker of cell death.

In addition to affecting DNA and nuclei, radiant energy may induce a variety of cytoplasmic changes including cytoplasmic swelling, mitochondrial distortion, and degeneration of the endoplasmic reticulum. Membrane breaks and focal defects may appear. The histologic constellation of cellular pleomorphism, changes in nuclei, and mitotic figures creates a more than passing similarity between injured cells and cancer cells, a problem that plagues the pathologist when evaluating the possible persistence of tumor cells.

At the light microscopic level, vascular changes and interstitial fibrosis are prominent (Fig. 8-14). During the immediate post-irradiation period, vessels may show only degenerative changes. At higher doses, a variety of degenerative changes appear, including endothelial cell swelling, dissolution with total necrosis of the walls of small vessels such as capillaries and venules, which may rupture or thrombose. Still later, endothelial cell proliferation and collagenous thickening of the media are seen in irradiated vessels, resulting in marked narrowing of the vascular lumina. At this time, an increase in interstitial collagen in the irradiated tissue is evident, leading to scarring and contractions.





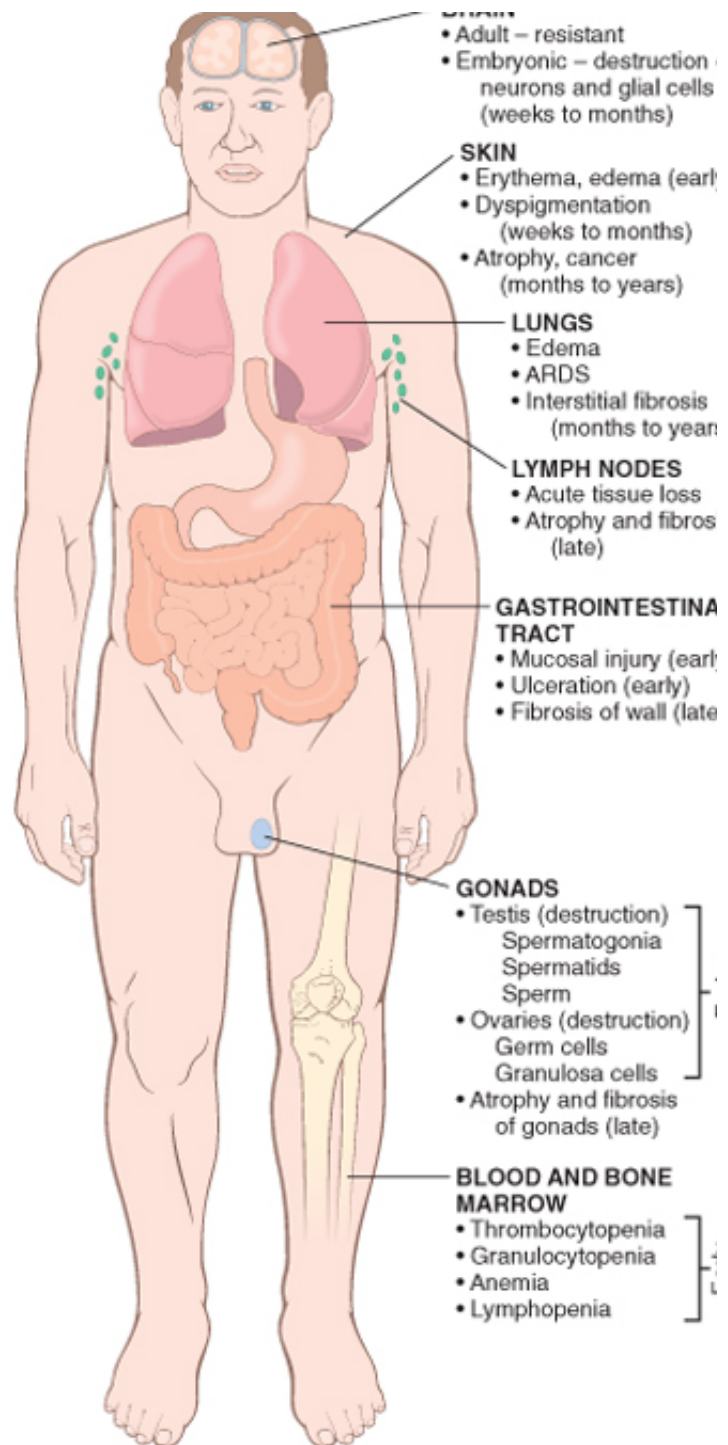
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Figure 8-14 Vascular changes and fibrosis of salivary glands produced by radiation therapy of the neck region. **A**, normal salivary gland; **B**, radiation; **C**, fibrosis and vascular changes consisting of fibrointimal thickening and arteriolar sclerosis. L, Vessel lumen. Upton, Department of Pathology, University of Washington, Seattle, Wash

### Effects on Organ Systems

**Figure 8-15** depicts the main consequences of radiation injury. As already mentioned, *the most sensitive are the hematopoietic and lymphoid systems, and the lining of the GI tract*. Estimated threshold doses for various organs are shown in **Table 8-7**. Here we briefly discuss the changes in the hematopoietic and lymphoid systems, and the lining of the GI tract. **Cancers induced by environmental or occupational exposure to ionizing radiation.**

**Hematopoietic and lymphoid systems.** The hematopoietic and lymphoid systems are extremely sensitive to radiation and deserve special mention. With high dose levels and large exposure fields, severe lymphopenia and atrophy of the lymph nodes and spleen occur. Radiation directly destroys lymphocytes in the blood and in tissues (nodes, spleen, thymus, gut). With sublethal doses of radiation, regrowth of lymphocytes occurs, leading to restoration of a normal lymphocyte count in the blood within weeks to months. The lymphocyte count rises but begins to fall toward the end of the first week. Levels near zero may be reached during the first week. If the patient survives, recovery of the normal granulocyte count may require 2 to 3 months. Platelet count occurs somewhat later than that of granulocytes; recovery is similarly delayed. Hematopoietic stem cells, including red cell precursors, are also quite sensitive to radiant energy. Erythrocytes are rare in the blood and appear after 2 to 3 weeks and persist for months because of marrow damage. **Environmental exposure and cancer.** Any cell capable of division that has sustained a mutation has the potential to become cancerous. Neoplasms may occur in any organ after exposure to ionizing radiation. The level of radiation-induced cancer development is difficult to determine; sublethal but relatively high doses are clearly associated with cancer. Documented by the increased incidence of leukemias and tumors at various sites (such as the atomic bombings of Hiroshima and Nagasaki, in the increase in thyroid cancers in survivors of the atomic bombings of Hiroshima and Nagasaki, in the increase in thyroid cancers in survivors of the atomic bombings of Hiroshima and Nagasaki, in the increase in thyroid cancers in survivors of the atomic bombings of Hiroshima and Nagasaki). **Occupational exposure and cancer.** The carcinogenic agents are two radon decay products ("radon daughters"), which emit alpha particles and have a short half-life. These particulate agents are inhaled during exposure in uranium miners may give rise to lung carcinomas. Risks are also present in homes with high radon levels, comparable to those found in mines. However, there is little or no evidence to suggest a significant risk of lung cancer in the average household.



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Figure 8-15 Overview of the major morphologic consequences of radiation injury. Early changes occur in hours to ARDS, acute respiratory distress syndrome.

**Table 8-7. Estimated Threshold Doses for Acute Radiation Effects on Specific**

Health Effect	Organ
Temporary sterility	Testes
Depression of hematopoiesis	Bone marrow



Reversible skin effects (e.g., erythema)	Skin
Permanent sterility	Ovaries
Temporary hair loss	Skin
Permanent sterility	Testis
Cataract	Lens of eye

### *Total-Body Irradiation*

Exposure of large areas of the body to even very small doses of radiation may have devastating effects, even with minimal or no symptoms. However, higher levels of exposure cause health effects known as acute radiation syndrome. Progressively higher doses involve the hematopoietic system, GI system, and CNS. The syndromes caused by ionizing radiation are presented in [Table 8-8](#).

### **SUMMARY**

**Radiation Injury** Ionizing radiation may injure the cells directly or indirectly by producing free radicals from water or molecular oxygen. Ionizing radiations damage DNA and therefore can cause mutations. Tissues such as germ cells, bone marrow and gastrointestinal tract are very sensitive to radiation damage. Damage that is not adequately repaired may result in mutations that predispose to cancer. Ionizing radiation may cause vascular damage and sclerosis of blood vessels, necrosis of parenchymal cells and their replacement by fibrous tissue.





## NUTRITIONAL DISEASES

Millions of people in undeveloped or developing nations starve or live on the cruel edge of starvation, struggle to avoid calories and the attendant obesity or fear that what they eat may contribute to at the lack of nutrition and overnutrition continue to be major health concerns.

**Table 8-8. Effects of Whole-Body Ionizing Radiation**

	0-1 Sv	1-2 Sv	2-10 Sv	10-20 Sv
Main site of injury	None	Lymphocytes	Bone marrow	Small bowel
Main signs and symptoms	-	Moderate leukopenia	Leukopenia, hemorrhage, epilation, vomiting	Diarrhea, fever, electrolyte imbalance, vomiting
Timing	-	1 day to 1 week	4-6 weeks	5-14 days
Lethality	-	None	Variable (0% to 80%)	100%

### Malnutrition

An appropriate diet should provide (1) sufficient energy, in the form of carbohydrates, fats, and proteins; (2) essential (as well as nonessential) [amino acids](#) and fatty acids to be used as building blocks for functional proteins and lipids; and (3) vitamins and minerals, which function as coenzymes or hormones. In the case of calcium and phosphate, as important structural components. In *primary malnutrition*, nutrients are missing from the diet. By contrast, in *secondary, or conditioned, malnutrition*, the supply of nutrients is reduced from nutrient malabsorption, impaired nutrient utilization or storage, excess nutrient losses, or increased requirements. Secondary malnutrition can be grouped into three general but overlapping categories: (1) GI disease, (2) acute critical illness.

Malnutrition is widespread and may be gross or subtle. Some common causes of dietary insufficiency are discussed below.

**Poverty.** Homeless persons, aged individuals, and children of the poor often suffer from protein and as trace nutrient deficiencies. In poor countries, poverty, together with droughts, crop failure, and displacement, setting for malnourishment of children and adults. **Ignorance.** Even the affluent may fail to recognize the needs of pregnant women have increased nutritional needs. Ignorance about the nutritional content of foods and examples are: (1) iron deficiency often develops in infants fed exclusively artificial milk diet instead of a diet may lack adequate amounts of thiamine, and (3) iodine is often lacking from food in inland areas, unless supplementation is provided. **Chronic alcoholism.** Alcoholic persons may so frequently lacking in several vitamins, especially thiamine, pyridoxine, folate, and [vitamin A](#). Deficiency, defective GI absorption, abnormal nutrient utilization and storage, increased metabolic requirements, and loss. A failure to recognize the likelihood of thiamine deficiency in patients with chronic alcoholism damage (e.g., Korsakoff psychosis, discussed in [Chapter 23](#)). **Acute and chronic illnesses.** Malnutrition is accelerated in many illnesses (in patients with extensive burns, it may double), resulting in increased requirements. Failure to recognize these nutritional needs may delay recovery. PEM is often protein deficiency (see below). **Self-imposed dietary restriction.** Anorexia nervosa, bulimia, and less overt eating disorders in individuals who are concerned about body image or suffer from an unreasonable fear of calories. Bulimia are discussed in a separate section in this chapter. **Other causes.** Additional causes of malnutrition are acquired and inherited malabsorption syndromes, specific drug therapies (which block uptake of nutrients) and total parenteral nutrition.

The sections that follow barely skim the surface of nutritional disorders. Particular attention is devoted to bulimia, deficiencies of vitamins and trace minerals, obesity, and a brief overview of the relationship between nutrients and nutritional issues are discussed in the context of specific diseases throughout the chapter.

Other nutrients and nutritional issues are discussed in the context of specific diseases throughout

### Protein-Energy Malnutrition (PEM)

Severe PEM is a serious, often lethal, disease. It is common in poor countries, where as many as where it is a major contributor to the high death rates among children younger than 5 years. In the suffered a severe famine in 2005, United Nation reports estimate that there are 150,000 children y malnourished and 650,000 who are moderately malnourished. In that country malnutrition is a dire children younger than age 5.

PEM presents as a range of clinical syndromes, all characterized by a dietary intake of protein and needs. The two ends of the spectrum of syndromes are known as *marasmus* and *kwashiorkor*. It is important to remember that from a functional standpoint, there are two protein compartments in the body: one represented by proteins in skeletal muscles, and the visceral compartment, represented by proteins in the liver. These two compartments are regulated differently, and, as we shall see, the somatic compartment is depleted more severely in marasmus, and the visceral compartment is depleted more severely in kwashiorkor. We first make an assessment of undernutrition and then discuss the clinical presentations of marasmus and kwashiorkor.

The most common victims of PEM worldwide are children. A child whose weight falls to less than 80% of normal for age is malnourished. The diagnosis of PEM is obvious in its most severe forms; in mild to moderate forms, the diagnosis is based on body weight for a given height with standard tables; other helpful parameters are the evaluation of skin and muscle. With a loss of fat, the thickness of skinfolds (which includes skin and subcutaneous tissue) is reduced. In marasmus, the visceral compartment is catabolized, the resultant reduction in muscle mass is reflected by reduced circumference of the arms and legs. Levels of serum proteins (albumin, transferrin, and others) provides a measure of the adequacy of protein intake.

A child is considered to have *marasmus* when weight level falls to 60% of normal for sex, height, and age. The loss of muscle mass results from catabolism and depletion of muscle proteins. The loss of muscle mass seems to be an adaptive response that provides the body with **amino acids** as a source of energy. The visceral compartment, which is presumably more precious and critical for survival, is depleted only marginally. In addition to muscle proteins, subcutaneous fat is also mobilized. In kwashiorkor, the rate of fat production is low, which may stimulate the hypothalamic-pituitary axis to produce more cortisol that contribute to lipolysis. With such losses of muscle and subcutaneous fat, the extremities appear too large for the body. Anemia and manifestations of multivitamin deficiencies are present. *deficiency*, particularly T-cell-mediated immunity. Hence, concurrent infections are usually present in an already weakened body.

*Kwashiorkor* occurs when protein deprivation is relatively greater than the reduction in total calories. It is the most common form of PEM seen in African children who have been weaned too early and subsequently fed, almost exclusively, a diet of cassava. The name kwashiorkor is from the Ga language in Ghana describing a disease of a baby due to the abrupt weaning. Kwashiorkor is also high in impoverished countries of Southeast Asia. Less severe forms may occur in children with diarrheal states in which protein is not absorbed or in those with chronic protein loss (e.g., protein-losing enteropathy, or the aftermath of extensive burns). Cases of kwashiorkor resulting from fad diets or from excessive alcohol consumption have been reported in the United States.





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 Figure 8-16 Kwashiorkor. The infant shows generalized edema, seen in the form of puffiness

In kwashiorkor (unlike in marasmus), marked protein deprivation is associated with severe loss of the resultant hypoalbuminemia gives rise to *generalized or dependent edema* (see Fig. 8-16). The kwashiorkor is typically 60% to 80% of normal. However, the true loss of weight is masked by the further contrast to marasmus, there is relative sparing of subcutaneous fat and muscle mass. The also be masked by edema. Children with kwashiorkor have characteristic *skin lesions*, with alternations of desquamation, and hypopigmentation, giving a "flaky paint" appearance. *Hair changes* include of pale and darker hair, straightening, fine texture, and loss of firm attachment to the scalp. Other marasmus include an enlarged, *fatty liver* (resulting from reduced synthesis of the carrier protein) development of apathy, listlessness, and loss of appetite. As in marasmus, vitamin deficiencies are *immunity* and *secondary infections*. In kwashiorkor, the physiologic stress brought about by infection motion a catabolic state that aggravates the malnutrition. It should be emphasized that marasmus spectrum, and considerable overlap exists.

*Secondary PEM* is not uncommon in chronically ill or hospitalized patients. A particularly severe form commonly develops in patients with advanced cancer (Chapter 6). The wasting is all too apparent of appetite may partly explain it, cachexia may appear before a decrease in appetite. A number of including an elevated resting metabolic rate and the production of cytokines such as TNF in response mobilization from lipid stores.

### Morphology

The central anatomic changes in PEM are (1) growth failure, (2) peripheral edema, loss of body fat and atrophy of muscle, more marked in marasmus.

The **liver** in kwashiorkor, but not in marasmus, is enlarged and fatty; superimposed on the fatty liver in kwashiorkor (rarely in marasmus) the **small bowel** shows a decrease in the mitoses of the glands, associated with mucosal atrophy and loss of villi and microvilli. In such cases, the small intestinal enzymes are deficient, most often manifested as disaccharidase deficiency. In kwashiorkor initially may not respond well to full-strength, milk-based diets. With treatment, the changes are reversible.

The **bone marrow** in both kwashiorkor and marasmus may be hypoplastic, mainly due to low numbers of red cell precursors. How much of this derangement is due to a deficiency of iron and how much to reduced synthesis of transferrin and ceruloplasmin is uncertain. At present, most often hypochromic microcytic anemia, but a concurrent deficiency of iron may produce a mixed microcytic-macrocytic anemia.

The **brain** in infants who are born to malnourished mothers and who suffer from PEM in the first years of life has been reported by some to show cerebral atrophy, a reduced number of neurons, and impaired myelination of white matter.

Many other changes may be present, including (1) thymic and lymphoid atrophy (more marked in kwashiorkor than in marasmus), (2) anatomic alterations induced by intercurrent infections in all manner of endemic worms and other parasites, and (3) deficiencies of other required nutrients such as iodine and vitamins.

### Anorexia Nervosa and Bulimia

*Anorexia nervosa* is self-induced starvation, resulting in marked weight loss; *bulimia* is a condition in which the patient then induces vomiting. Bulimia is more common than anorexia nervosa and generally has a better prognosis. It affects about 2% of women and 0.1% of men, with an average onset at 20 years of age. These eating disorders are most common in young women who have developed an obsession with attaining thinness.

The clinical findings in anorexia nervosa are generally similar to those in severe PEM. In addition, the menstrual cycle is often absent (*amenorrhea*), resulting from decreased secretion of gonadotropin-releasing hormone (and luteinizing and follicle-stimulating hormones), is so common that its presence is a diagnostic feature. Other findings, related to decreased thyroid hormone release, include cold intolerance, bradycardia, constipation, and brittle hair. In addition, dehydration and electrolyte abnormalities are frequently present. The skin becomes dry and scaly as a result of excess carotene in the blood. Body hair may be increased but is usually fine and pale (likely because of low estrogen levels, which mimics the postmenopausal acceleration of osteoporosis). Anemia, lymphopenia, and hypoalbuminemia may be present. A major complication of anorexia nervosa is cardiac arrhythmia and sudden death, resulting in all likelihood from hypokalemia.

In bulimia, binge eating is the norm. Huge amounts of food, principally carbohydrates, are ingested and then vomited. Although menstrual irregularities are common, amenorrhea occurs in fewer than 50% of patients. Weight and gonadotropin levels are maintained near normal. The major medical complications are chronic use of laxatives and diuretics. These include (1) electrolyte imbalances (hypokalemia), with cardiac arrhythmias; (2) pulmonary aspiration of gastric contents; and (3) esophageal and stomach rupture. The signs and symptoms for this syndrome, and the diagnosis must rely on a comprehensive psychological evaluation.

### Vitamin Deficiencies

Thirteen vitamins are necessary for health; four (A, D, E, and K) are fat-soluble, and the remainder are water-soluble. The distinction between fat- and water-soluble vitamins is important; although the former are more readily stored in fat, malabsorption disorders, caused by disturbances of digestive functions (discussed in [Chapter 14](#)), can lead to deficiencies. Vitamin D is synthesized endogenously from precursor steroids, vitamin K and biotin by the intestine from essential amino acids. Notwithstanding this endogenous synthesis, a dietary supply of all vitamins is necessary for health.



an essential amino acid. Notwithstanding this endogenous synthesis, a dietary supply of all vitamins

A deficiency of vitamins may be primary (dietary in origin) or secondary (because of disturbances in blood, tissue storage, or metabolic conversion). In the following sections, vitamins A, D, and C are discussed in terms of their wide-ranging functions and the morphologic changes of deficient states. This is followed by a discussion of the consequences of deficiencies of the remaining vitamins (E, K, and the B complex) and some essential points emphasized that deficiency of a single vitamin is uncommon and that single- or multiple-vitamin deficiencies are concurrent PEM.

## Vitamin A

The fat-soluble **vitamin A** is a generic name for a group of related compounds that include *retinoids* with similar biologic activities. Retinol is the chemical name given to **vitamin A**. It is the transport form of vitamin A. A widely used term, *retinoids*, refers to both natural and synthetic chemicals that are structurally similar and necessarily have **vitamin A** activity. Animal-derived foods such as liver, fish, eggs, milk, and butter contain preformed **vitamin A**. Yellow and leafy green vegetables such as carrots, squash, and spinach contain provitamins, many of which are provitamins that can be metabolized to active **vitamin A** in the body. Carotenoids are the most important of these in human diets; the most important of these is  $\beta$ -carotene, which is efficiently converted to active **vitamin A**. Dietary allowance for **vitamin A** is expressed in retinol equivalents, to take into account both preformed and provitamin sources.

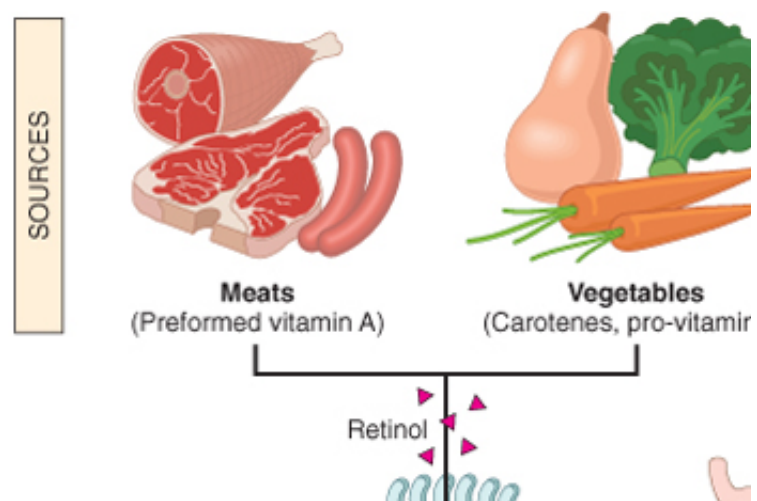
As with all fats, the digestion and absorption of carotenoids and retinoids require bile, pancreatic enzyme, and activity in the food. Retinol (generally ingested as retinol ester) and  $\beta$ -carotene are absorbed through the intestinal mucosa and is converted to retinol (Fig. 8-17). Retinol is then transported in chylomicrons to the liver for esterification. Retinol takes place through the apolipoprotein E receptor. More than 90% of the body's **vitamin A** reserve is stored in the perisinusoidal stellate (Ito) cells. In healthy persons who consume an adequate diet, these reserves can last for several months of **vitamin A** deprivation. Retinol esters stored in the liver can be mobilized; before release, they are bound to retinol-binding protein (RBP), synthesized in the liver. The uptake of retinol/RBP in peripheral tissues is dependent on specific receptors for RBP rather than for retinol. After uptake by these cells, retinol binds to a cellular RBP, forming a retinol-RBP complex. Retinol may be stored in peripheral tissues as retinyl ester or be oxidized to form retinoic acid.

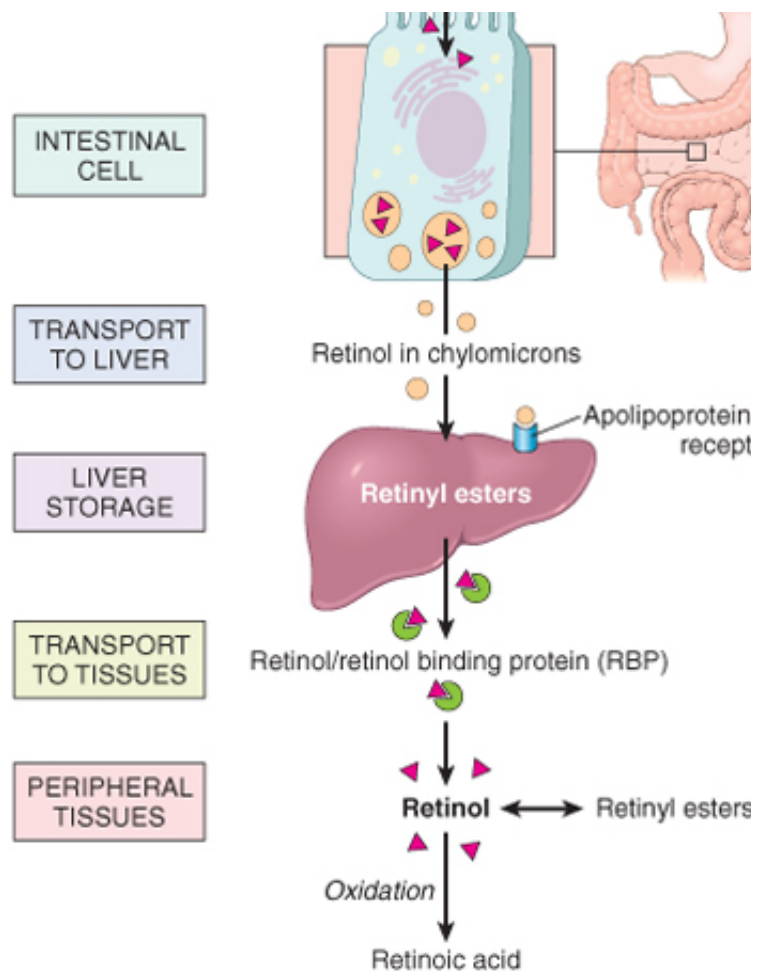
## Function

In humans, the best-defined functions of **vitamin A** are

- Maintaining normal vision in reduced light
- Potentiating the differentiation of specialized epithelial cells
- Enhancing immunity to infections, particularly in children with measles.

In addition, the retinoids,  $\beta$ -carotene, and some related carotenoids can function as photoprotective agents. They have broad biologic effects, including effects on embryonic development, cellular differentiation and proliferation, and regulation of gene expression.





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Figure 8-17 Vitamin A<sub>R</sub> metabolism.

The *visual process* involves four forms of vitamin A-containing pigments: rhodopsin in the rods, which is important in reduced light; and three iodopsins in cone cells, each responsive to a different wavelength of light. The conversion of retinol to rhodopsin involves (1) oxidation to all-*trans*-retinal, (2) isomerization to 11-*cis*-retinal, and (3) binding to opsin, to form rhodopsin. A photon of light causes the isomerization of 11-*cis*-retinal to all-*trans*-retinal, which produces a visual signal. In the process, a nerve impulse is generated and transmitted via neurons from the retina to the brain. During dark adaptation, some of the all-*trans*-retinal is reduced to retinol and lost to the retina, dictating the need for continuous supply of retinol.

Vitamin A and retinoids play an important role in the orderly *differentiation of mucus-secreting epithelium*. When the epithelium undergoes squamous metaplasia and differentiation to a keratinizing epithelium. All-trans-retinoic acid (ATRA), exerts its effects by binding to retinoic acid receptors (RARs). These receptors bind to 9-*cis*-retinoic acid (RXR), forming RAR/RXR heterodimers. The RAR/RXR heterodimers act as transcription factors, binding to specific DNA elements present in the promoter region of multiple genes that encode cell receptors and secretory factors, and tumor suppressor genes. ATRA induces temporary remission of promyelocytic leukemia. The Philadelphia chromosome translocation (Chapter 12) results in the fusion of a truncated *RAR-α* gene on chromosome 17 with the *Bcr* gene on chromosome 22. The fusion gene encodes an abnormal RAR that blocks myeloid cell differentiation. Pharmacologic doses of ATRA induce neutrophil differentiation. Although this "differentiation therapy" induces remission in most patients, patients ultimately develop resistance to ATRA. The retinoic acid isomer 13-*cis* retinoic acid has been used to treat neuroblastomas in children. Retinoic acid, it should be noted, has no effect on vision.

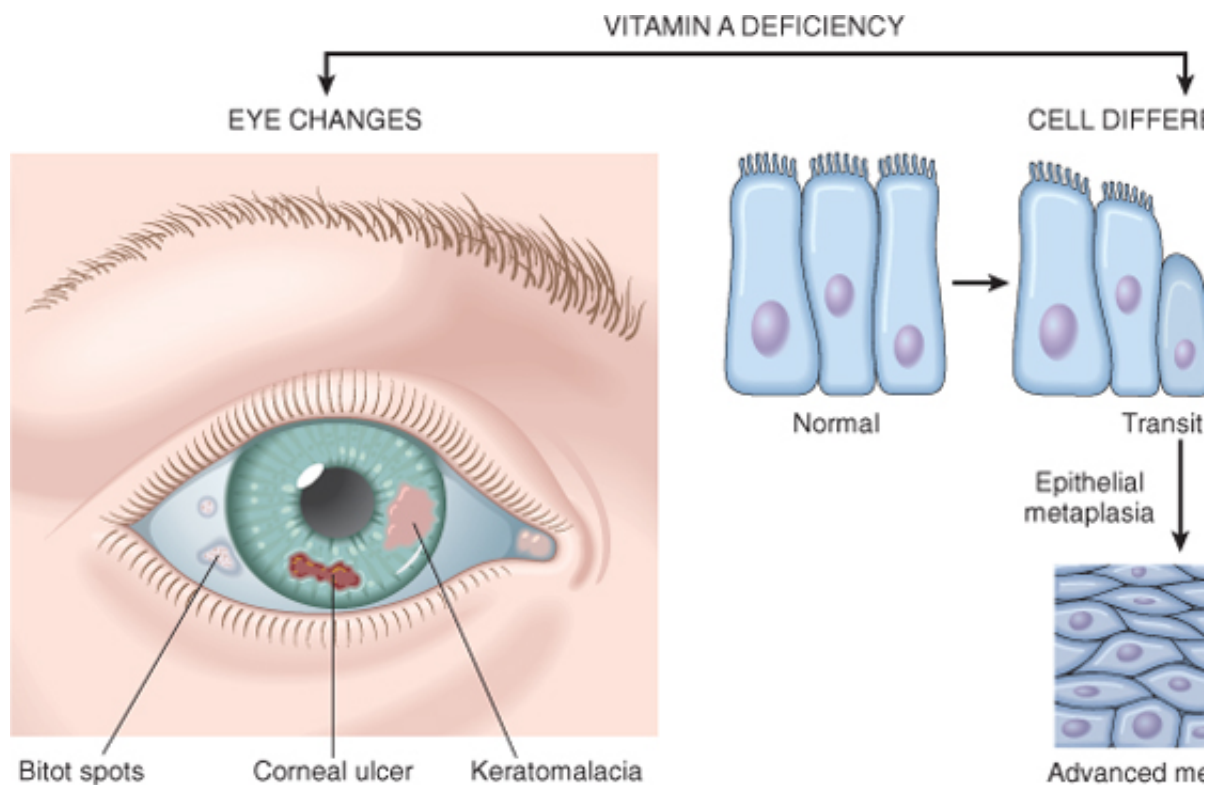
Vitamin A plays a role in host *resistance to infections*. Vitamin A<sub>R</sub> supplementation can reduce mortality in children with severe malnutrition.

Vitamin A plays a role in host resistance to infections. Vitamin A supplementation can reduce the incidence of diarrhea, and supplementation in preschool children with measles can quickly improve the clinical course. The protective effect of vitamin A in diarrheal diseases may be related to the maintenance and restoration of the integrity of the intestinal mucosa. The effects of vitamin A on infections derive in part from its ability to stimulate the immune system, probably through its role in the development of immunity, although the mechanisms are unclear. Another aspect of the relationship between vitamin A and infections is its ability to reduce the bioavailability of vitamin A. One possible mechanism for this effect is the inhibition of the acute phase response associated with many infections. The drop in hepatic RBP causes a decrease in the tissue availability of vitamin A.

### Deficiency States

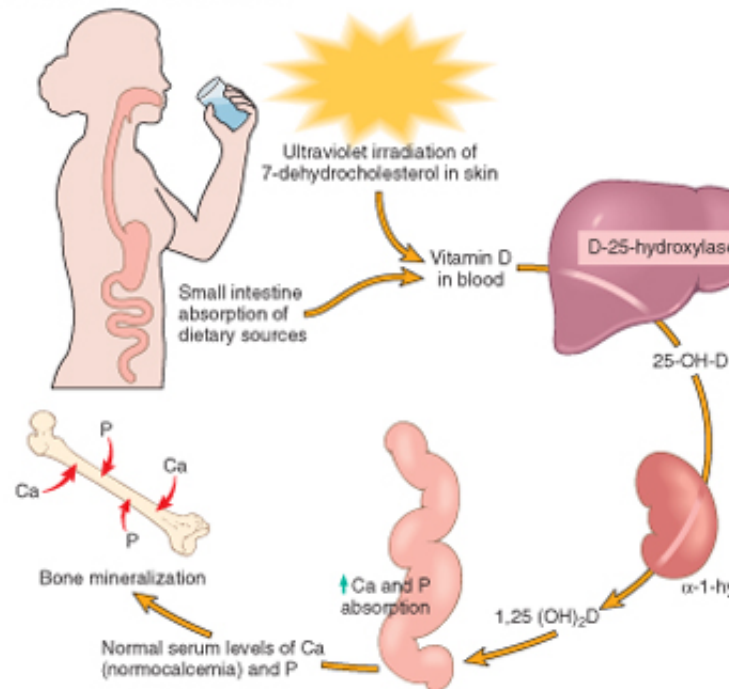
Vitamin A deficiency occurs worldwide either as a consequence of general poor nutrition or as a result of conditions that cause malabsorption of fats. In children, stores of vitamin A are depleted by infections and poor nutrition. In adults, patients with malabsorption syndromes, such as celiac disease, have vitamin A deficiency, in conjunction with depletion of other fat-soluble vitamins. Bariatric surgery or the use of mineral oil as laxative may lead to deficiency.

As was already discussed, vitamin A is a component of rhodopsin and other visual pigments. No manifestations of vitamin A deficiency are related to the role of vitamin A in maintaining the differentiation of epithelial cells (e.g., the cornea). The most devastating manifestations of vitamin A deficiency are related to the role of vitamin A in maintaining the differentiation of epithelial cells (e.g., the cornea). The most devastating manifestation of vitamin A deficiency is xerophthalmia (dry eye). First, there is dryness of the conjunctiva (xerosis conjunctivae) and the mucin-secreting epithelium is replaced by keratinized epithelium. This is followed by buildup of keratin deposits (Bitot spots) and, eventually, erosion of the roughened corneal surface with softening and destruction of the cornea (keratomalacia) and blindness.

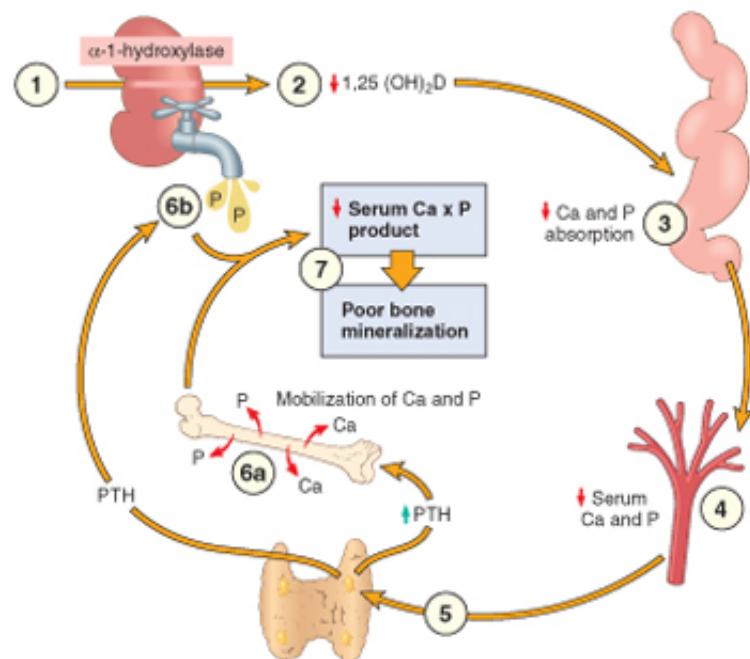


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 Figure 8-18 Vitamin A deficiency: its major consequences in the eye and in the production of keratinizing metaplasia. Not depicted are night blindness and immunodeficiency.

### A. NORMAL VITAMIN D METABOLISM



### B. VITAMIN D DEFICIENCY



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Figure 8-19 **A**, Normal vitamin D metabolism. **B**, Vitamin D deficiency. There is inadequate substrate for the  $1,25(\text{OH})_2\text{D}$  (2), and deficient absorption of calcium and phosphorus from the gut (3), with consequent depression of serum calcium and phosphorus (4). This activates the parathyroid glands (5), causing mobilization of calcium and phosphorus from bone (6a). Simultaneous wasting of phosphate in the urine (6b) and calcium retention. Consequently, the serum levels of calcium are normal, but the serum levels of phosphorus are low, hence, mineralization is impaired (7).

In addition to the ocular epithelium, the epithelium lining the upper respiratory passage and urinary squamous cells (*squamous metaplasia*). Loss of the mucociliary epithelium of the airways predisposes to renal and urinary bladder squamous metaplasia.

*hyperkeratinization of the epidermis* with plugging of the ducts of the adnexal glands may produce very serious consequence of lack of **vitamin A**. Immune deficiency. This impairment of immunity common infections such as measles, pneumonia, and infectious diarrhea. In parts of the world where prevalent, dietary supplements reduce mortality by 20% to 30%.

In passing, we should note that despite past enthusiasms for the intake of megadoses of **vitamin A**, current evidence indicates that **vitamin A** and carotenes offer no protection from lung cancer.

#### *Vitamin A Toxicity*

Both short- and long-term excesses of **vitamin A** may produce toxic manifestations, a point of caution touted by certain sellers of supplements. The consequences of acute hypervitaminosis A were first described by a ship's carpenter stranded in the Arctic, who recounted in his diary the serious symptoms that he experienced after eating polar bear liver. Keeping this in mind, eat with moderation when served this delicacy, which has also been described in individuals who ingested livers of whales, sharks, and even the lowly turbot. Toxicity includes headache, dizziness, vomiting, stupor, and blurred vision, symptoms that may be relieved by stopping intake. Chronic toxicity is associated with weight loss, anorexia, nausea, vomiting, and bone and joint pain. Retinoid treatment of acne are not associated with these complications, their use in pregnancy should be avoided because of the effect of retinoids in increasing the risk of fetal malformations.

#### **Vitamin D**

The major function of the fat-soluble vitamin D is the maintenance of normal plasma levels of calcium required for the prevention of bone diseases known as *rickets* (in children whose epiphyses have not matured) and hypocalcemic tetany. With respect to tetany, vitamin D maintains the correct concentration of calcium in the extracellular fluid compartment required for normal neural excitation and relaxation of muscle. Insufficient calcium in the extracellular fluid results in continuous excitation of muscle, leading to the convulsive state, hypocalcemia. This section focuses on the function of vitamin D in the regulation of serum calcium levels.

#### *Metabolism of Vitamin D*

The major source of vitamin D for humans is its endogenous synthesis in the skin by photochemical conversion of 7-dehydrocholesterol, via the energy of solar or artificial UV light. Irradiation of this compound forms vitamin D<sub>3</sub> (cholecalciferol). For the sake of simplicity we will use the term vitamin D to refer to this compound. Under usual conditions, the vitamin D needed is endogenously derived from 7-dehydrocholesterol present in the skin. However, in some individuals, vitamin D production in the skin because of melanin pigmentation. The small remainder comes from dietary sources: fish, plants, and grains; this requires normal fat absorption. In plant sources, vitamin D is present as ergosterol, which is converted to vitamin D in the body.

The metabolism of vitamin D can be outlined as follows (Fig. 8-19):

1. Absorption of vitamin D along with other fats in the gut or synthesis from precursors in the skin
2. Binding to plasma  $\alpha_1$ -globulin (D-binding protein) and transport to liver
3. Conversion to 25-hydroxyvitamin D (25-OH-D) by 25-hydroxylase in the liver
4. Conversion of 25-OH-D to 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{-D}$ ] by  $\alpha_1$ -hydroxylase in the kidney (the active form of vitamin D).

The production of  $1,25(\text{OH})_2\text{-D}$  by the kidney is regulated by three mechanisms:

*Hypocalcemia stimulates secretion of parathyroid hormone (PTH), which in turn augments the production of  $1,25(\text{OH})_2\text{-D}$  by activating  $\alpha_1$ -hydroxylase. Hypophosphatemia directly activates  $\alpha_1$ -hydroxylase and through a feedback loop, increased levels of  $1,25(\text{OH})_2\text{-D}$  down-regulate synthesis of this metabolite. Conversely, a decrease in the levels of  $1,25(\text{OH})_2\text{-D}$  has the opposite effect.*



### Functions of Vitamin D

1,25(OH)<sub>2</sub>-D, the biologically active form of vitamin D, is best regarded as a steroid hormone. Like to a high-affinity nuclear receptor that in turn binds to regulatory DNA sequences, which induce target proteins. The receptors for 1,25-(OH)<sub>2</sub>-D are present in most nucleated cells of the body, and various biologic activities, beyond those involved in calcium and phosphorus homeostasis. Nevertheless, vitamin D relates to the maintenance of normal plasma levels of calcium and phosphorus, through kidneys (see Fig. 8-19).

The active form of vitamin D

Stimulates intestinal absorption of calcium and phosphorus  
Collaborates with PTH in the maintenance of bone  
Stimulates the PTH-dependent reabsorption of calcium in renal distal tubules.

We now consider these three functions of vitamin D.

How 1,25(OH)<sub>2</sub>-D stimulates *intestinal absorption of calcium and phosphorus* is still somewhat unclear. It is viewed that it binds to the nuclear vitamin D receptor, activating the synthesis of proteins that participate in the transport of calcium and phosphorus from the intestinal lumen into the bloodstream. The increased absorption of phosphorus is independent of that of calcium.

*The effects of vitamin D on bone depend on the plasma levels of calcium.* On the one hand, with PTH, it promotes the resorption of calcium and phosphorus from bone to support blood levels. On the other hand, it promotes the normal mineralization of epiphyseal cartilage and osteoid matrix. It is still not clear how the resorption is ruled out. More likely, vitamin D favors the formation of osteoclasts from mononuclear precursors by influencing the production of RANK (receptor activator of NF-κB) ligand (Chapter 21). The precise mechanism by which vitamin D levels are adequate are also uncertain. The main function of vitamin D may be to maintain calcium levels in the plasma. However, vitamin D clearly activates osteoblasts to synthesize osteocalcin, involved in the deposition of calcium into osteoid matrix, and may thus contribute to bone formation.

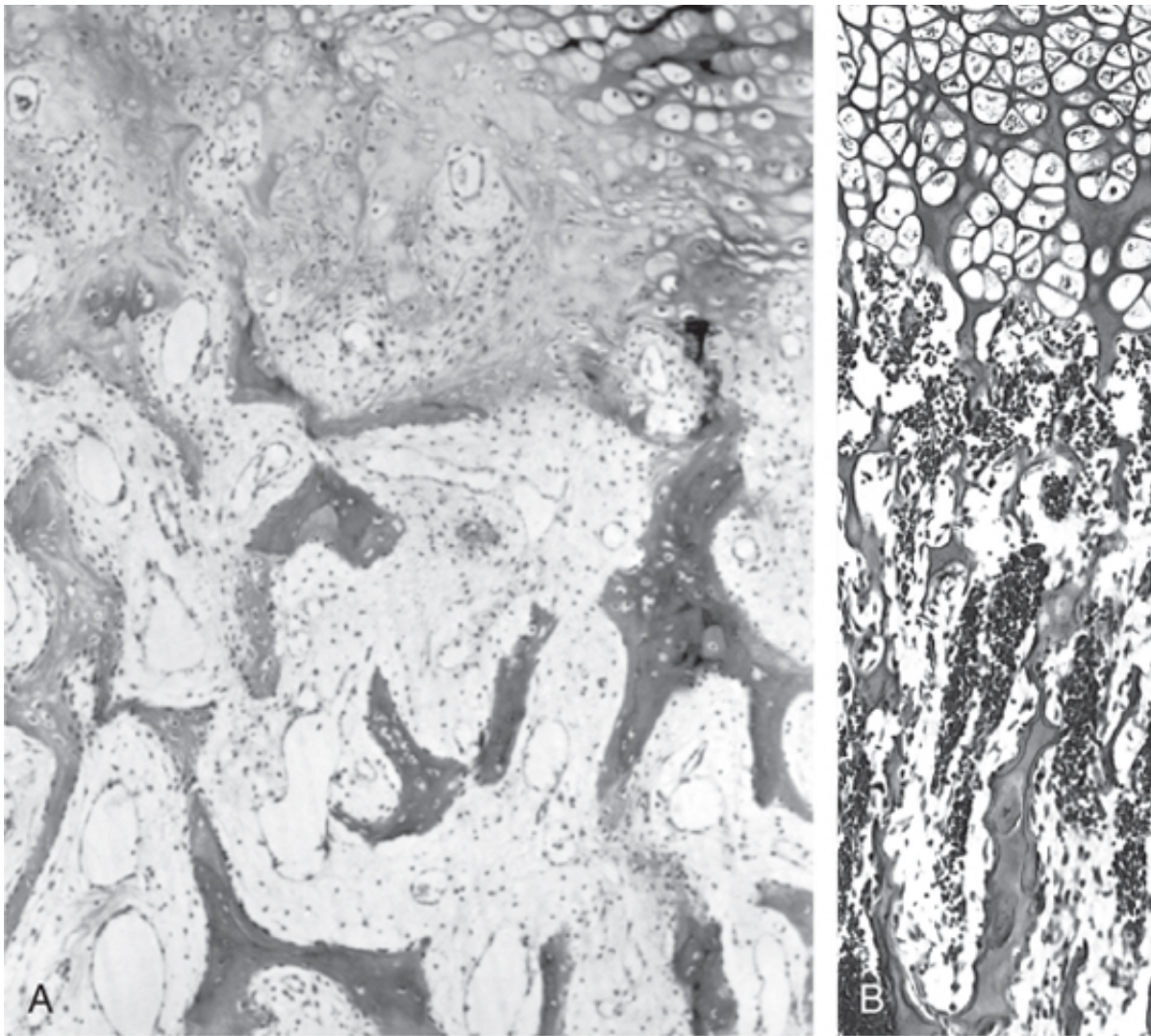
Equally unclear is the role of vitamin D in renal *reabsorption of calcium*. PTH is clearly necessary, but there is substantial evidence that vitamin D participates in renal reabsorption of phosphorus.

### Deficiency States

Rickets in growing children and osteomalacia in adults are skeletal diseases with worldwide distribution. They are caused by a deficiency in calcium and vitamin D, but probably more important is limited exposure to sunlight (for children born to mothers who have frequent pregnancies followed by lactation that causes vitamin D deficiency; for adults, living in climates with scant sunlight). Other less common causes of rickets and osteomalacia include renal failure, deficiency of 1,25 (OH)<sub>2</sub>-D or phosphate depletion and malabsorption disorders. Although rickets and osteomalacia are severe forms of vitamin D deficiency (also called vitamin D insufficiency) leading to bone loss, milder forms of deficiency are also seen in the elderly. Whatever the basis, a deficiency of vitamin D tends to cause hypocalcemia. When hypocalcemia is increased, which (1) activates renal α<sub>1</sub>-hydroxylase, thus increasing the amount of active vitamin D, (2) increases renal calcium reabsorption, (3) decreases renal calcium excretion, and (4) increases renal excretion of phosphate, calcium is restored to near normal, but hypophosphatemia persists, and so mineralization of bone is impaired.

An understanding of the morphologic changes in rickets and *osteomalacia* is facilitated by a brief review of bone development and maintenance. The development of flat bones in the skeleton involves intramembranous ossification. The development of long bones reflects endochondral ossification. With intramembranous bone formation, mesenchymal cells differentiate into osteoblasts, which synthesize the collagenous osteoid matrix on which calcium is deposited. In contrast, with endochondral ossification, cartilage at the epiphyseal plates is provisionally mineralized and then progressively resorbed and replaced by bone, which undergoes mineralization to create bone (Fig. 8-20).





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 Figure 8-20 Rickets. **A**, Detail of costochondral junction in which the palisade of cartilage is lost. Darker trabeculae uncalcified osteoid. **B**, Compare with normal costochondral junction of a young child. Note cartilage palisade forming bone.

### Morphology

**The basic derangement in both rickets and osteomalacia is an excess of unmineralized osteoid.** The changes that occur in the growing bones of children with rickets, however, are characterized by the failure of provisional calcification of epiphyseal cartilage, deranging endochondral bone growth. The sequence ensues in rickets:

- Overgrowth of epiphyseal cartilage due to inadequate provisional calcification
- Persistence of distorted, irregular cartilage cells to mature and disintegrate
- Distorted cartilage cells of which project into the marrow cavity
- Deposition of osteoid matrix on inadequately calcified cartilaginous remnants
- Disruption of the orderly replacement of cartilage by bone
- Enlargement and lateral expansion of the osteochondral junction (Fig. 8-20)
- Disorganized zone resulting from microfractures
- Inadequately mineralized, weak, poorly formed bone
- Deformation of the skeletal structure
- Loss of structural rigidity of the developing bones

The gross skeletal changes depend on the severity of the rachitic process; its duration; and the stresses to which individual bones are subjected. During the nonambulatory stage,

stresses to which individual bones are subjected. During the nonambulatory stage chest sustain the greatest stresses. The softened occipital bones may become flat bones can be buckled inward by pressure; with the release of the pressure, elastic back into their original positions (**craniotabes**). An excess of osteoid produces **frontal squaring** appearance to the head. Deformation of the chest results from overgrowth tissue at the costochondral junction, producing the "**rachitic rosary**." The weakened ribs are subject to the pull of the respiratory muscles and thus bend inward, create the sternum (**pigeon breast deformity**). The inward pull at the margin of the diaphragm creates the **Harrison groove**, girdling the thoracic cavity at the lower margin of the rib cage. The chest is deformed. When an ambulating child develops rickets, deformities are likely to affect long bones (e.g., tibia), causing, most notably, **lumbar lordosis** and **bowing of the**

In adults the lack of vitamin D deranges the normal bone remodeling that occurs the formed osteoid matrix laid down by osteoblasts is inadequately mineralized, thus produces a persistent osteoid that is characteristic of osteomalacia. Although the contours of the bone is weak and vulnerable to gross fractures or microfractures, which are microfractures and femoral necks.

Histologically, the unmineralized osteoid can be visualized as a thickened layer of osteoid (in hematoxylin and eosin preparations) arranged about the more basophilic, normally mineralized bone. Studies also suggest that vitamin D may be important for preventing demineralization of bone minerals with aging. In certain familial forms of osteoporosis ([Chapter 21](#)), the defect is localized to the vitamin D receptor.







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Figure 8-21 Rickets. Note bowing of legs due to the formation of poorly mineralized bone.

### *Vitamin D Toxicity*

Prolonged exposure to normal sunlight does not produce an excess of vitamin D, but megadoses of vitamin D (hypervitaminosis D) can be harmful. Hypervitaminosis D may take the form of metastatic calcifications of soft tissue, bone pain, and hypercalcemia. In passing, we might point out that the toxic potential of this vitamin is a potent rodenticide!

### **Vitamin C (Ascorbic Acid<sub>Rx</sub>)**

A deficiency of water-soluble vitamin C leads to the development of *scurvy*, characterized principally by hemorrhages and healing defects in both children and adults. Sailors of the British Royal Navy at the end of the 18th century the Navy began to provide lime and lemon juice to sailors to prevent scurvy. It was not until 1932 that **ascorbic acid<sub>Rx</sub>** was identified and synthesized. **Ascorbic acid<sub>Rx</sub>** is not synthesized in the body; therefore we are entirely dependent on the diet for this nutrient. **Ascorbic acid<sub>Rx</sub>** is present in milk and is abundant in a variety of fruits and vegetables. All but the most restricted diets provide adequate amounts of vitamin C.

### *Function*

Ascorbic acid functions in a variety of biosynthetic pathways by accelerating hydroxylation and an established function of vitamin C is the activation of prolyl and lysyl hydroxylases from inactive precursors. Inadequately hydroxylated pro-collagen cannot acquire a stable helical configuration so it is poorly secreted from the fibroblasts. Those molecules that are secreted lack tensile strength and are vulnerable to enzymatic degradation. Collagen, which normally has the highest content of hydroxyproline and hydroxylysine in blood vessels, accounting for the predisposition to hemorrhages in scurvy. In addition, it appears that there is a suppression of the rate of synthesis of collagen peptides, independent of an effect on proline hydroxylation.

While the role of vitamin C in collagen synthesis has been known for many decades, it is only in recent years that its role has been recognized. Vitamin C can scavenge free radicals directly and can act indirectly by regenerating other antioxidants.

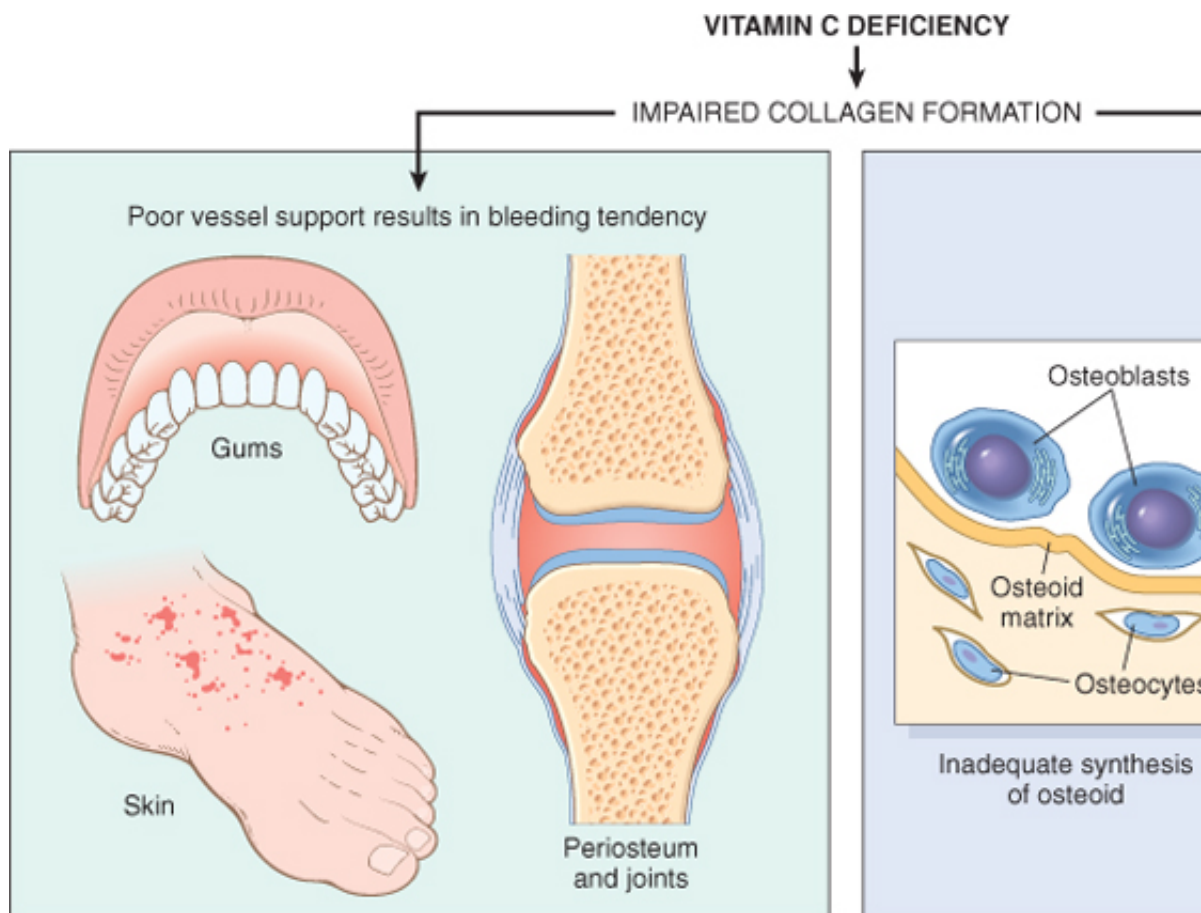
### *Deficiency States*

Consequences of vitamin C deficiency are illustrated in [Figure 8-22](#). Fortunately, because of the availability of vitamin C in foods, scurvy has ceased to be a global problem. It is sometimes encountered even in affluent populations, particularly among elderly individuals, persons who live alone, and chronic alcoholics—groups that have certain dietary patterns. Occasionally, scurvy appears in patients undergoing peritoneal dialysis and hemodialysis.

### Vitamin C Toxicity

The popular notion that megadoses of vitamin C protect against the common cold or at least allay controlled clinical studies. Such slight relief as may be experienced is probably a result of the mild. The large excess of vitamin C is promptly excreted in the urine, but may cause uricosuria and increased potential of iron overload.

Other vitamins and some essential minerals are listed and briefly characterized in [Tables 8-9](#) and discussed in [Chapter 12](#).



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Figure 8-22 Major consequences of vitamin C deficiency caused by impaired formation of collagen. They include poor vessel support, inadequate formation of osteoid matrix, and impaired wound healing.

### SUMMARY

**Nutritional Diseases** Primary protein-energy malnutrition (PEM) is a common cause of mortality in poor countries. The two main primary PEM syndromes are marasmus and kwashiorkor. Secondary PEM occurs in chronically ill and advanced cancer patients (cachexia), characterized by hypoalbuminemia, generalized edema, fatty liver, skin changes, and decreased immunity. It is caused by diets low in proteins but normal in calories. Marasmus is characterized by emaciation resulting from loss of muscle mass and fat with relative preservation of internal organs. It is caused by diets severely lacking in calories—both protein and non-protein. Anorexia nervosa is induced starvation; it is characterized by amenorrhea and multiple consequences on endocrine hormone levels. Bulimia is a condition in which food binges alternate with periods of self-induced vomiting. Vitamins A and D are fat-soluble vitamins with a wide-range of activities. Vitamin C and the B vitamins are water-soluble (consult [Table 8-9](#) for a listing of vitamin functions and deficiencies).



syndromes).

## Obesity

More than half of Americans between 20 and 75 years of age are overweight. Because obesity is the incidence of several diseases (e.g., diabetes, hypertension), it is important to define and recognize it in order to be able to initiate appropriate measures to prevent it or to treat it.

Obesity is defined as a state of increased body weight, due to adipose tissue accumulation, that is associated with adverse health effects. How does one measure fat accumulation? There are several highly technical methods of measurement, but for practical purposes the following are commonly used:

Some expression of weight in relation to height, such as the measurement referred to as the body mass index (BMI) ( $\text{kg/m}^2$ )  
 Skinfold measurements  
 Various body circumferences, particularly waist circumference

The BMI, expressed in kilograms per square meter, is closely correlated with body fat. A BMI of 18.5 or less is considered normal. It is generally agreed that a 20% excess in body weight ( $\text{BMI} > 27 \text{ kg/m}^2$ ) imparts a health risk.

**Table 8-9. Vitamins: Major Functions and Deficiency Syndromes**

Vitamin	Functions	Deficiency Syndrome
<b>Fat-Soluble</b>		
Vitamin A <sub>Rx</sub>	A component of visual pigment	Night blindness, xerophthalmia
	Maintenance of specialized epithelia	Squamous metaplasia
	Maintenance of resistance to infection	Vulnerability to infection
Vitamin D	Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone	Rickets in children (osteomalacia in adults)
Vitamin E <sub>Rx</sub>	Major antioxidant; scavenges free radicals	Spinocerebellar degeneration
Vitamin K	Cofactor in hepatic carboxylation of procoagulants - factors II (prothrombin), VII, IX, and X; and protein C and protein S	Bleeding diathesis
<b>Water-Soluble</b>		
Vitamin B <sub>1</sub> (thiamine)	As pyrophosphate, is coenzyme in decarboxylation reactions	Dry and wet beriberi syndrome
Vitamin B <sub>2</sub> (riboflavin)	Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism	Ariboflavinosis, cheilosis, corneal vascularization
Niacin <sub>Rx</sub>	Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate, involved in a variety of redox reactions	Pellagra - "three Ds"
Vitamin B <sub>6</sub> (pyridoxine)	Derivatives serve as coenzymes in many intermediary reactions	Cheilosis, glossitis, dermatitis
Vitamin B <sub>12</sub>	Required for normal folate metabolism and DNA synthesis Maintenance of myelination of spinal cord tracts	Combined system degeneration (anemia and degeneration of spinal cord tracts)
Vitamin C	Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen	Scurvy
Folate	Essential for transfer and use of 1-carbon units in DNA synthesis	Megaloblastic anemia
Pantothenic acid	Incorporated in coenzyme A	No nonexperimental deficiency
Biotin	Cofactor in carboxylation reactions	No clearly defined deficiency

The untoward effects of obesity are related not only to the total body weight but also to the distribution of fat.

*obesity*, in which fat accumulates in the trunk and in the abdominal cavity (in the mesentery and a higher risk for several diseases than is excess accumulation of fat diffusely in subcutaneous tissue).

The etiology of obesity is complex and incompletely understood. Involved are genetic, environmental, and behavioral factors. Simply put, obesity is a disorder of energy balance. The two sides of the energy equation, intake and expenditure, are regulated by neural and hormonal mechanisms, and body weight is thus maintained within a narrow range for a given individual. Intake is maintained by an internal set point, or "lipostat," that can sense the quantity of energy stores (adipose tissue) and adjust food intake as well as energy expenditure. In recent years, several "obesity genes" have been identified that encode the molecular components of the physiologic system that regulates energy balance. A key gene and its product, *leptin*. This unique member of the cytokine family, secreted by adipocytes, regulates the energy equation—intake of food and expenditure of energy. As discussed below, *the net effect of leptin is to increase energy expenditure*.

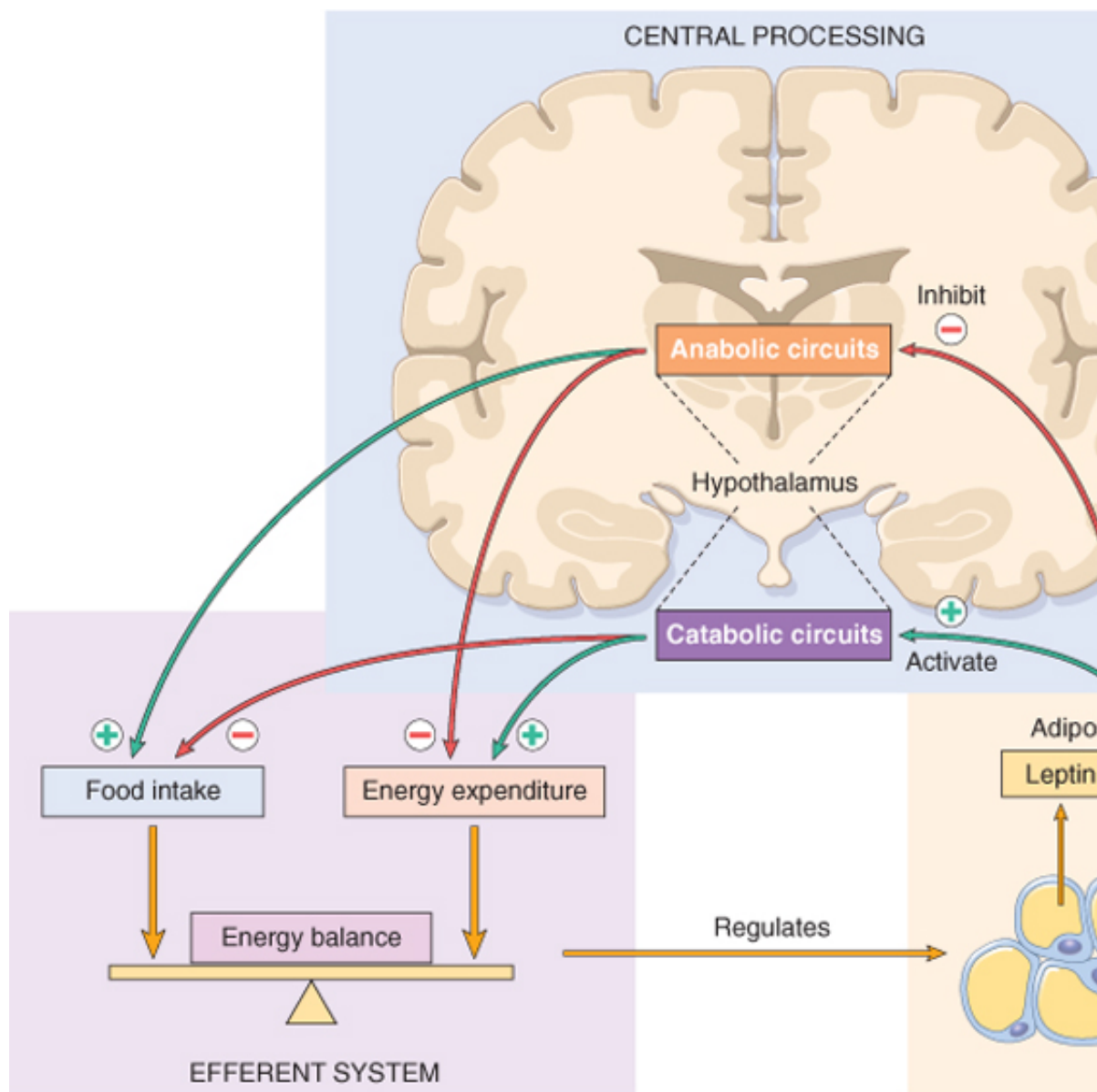
The neurohumoral mechanisms that regulate energy balance and body weight are very complex (Figure 8-10). These mechanisms may be divided into three components:

The afferent system, which generates signals from various sites. Its main components are *ghrelin* (stomach), and *peptide YY* (ileum and colon). Leptin reduces food intake and is also known to stimulate appetite, and it may function as a "meal-initiating signal." Peptide YY, which is released in the ileum and colon, is a satiety signal. The hypothalamus processing system known as the arcuate nucleus integrates the different types of afferent signals and generates efferent signals. The efferent signals are generated in the hypothalamus, which control food intake and energy expenditure.

## Leptin

**Table 8-10. Selected Trace Elements and Deficiency Syndromes**

Element Function		Basis of Deficiency
Zinc	Component of enzymes, principally oxidases	Inadequate supplementation in artificial diets
		Interference with absorption by other dietary constituents
		Inborn error of metabolism
Iron	Essential component of hemoglobin as well as several iron-containing metalloenzymes	Inadequate diet Chronic blood loss
Iodine	Component of thyroid hormone	Inadequate supply in food and water
Copper	Component of cytochrome c oxidase, dopamine β-hydroxylase, tyrosinase, lysyl oxidase, and unknown enzyme involved in cross-linking collagen	Inadequate supplementation in artificial diet Interference with absorption
Fluoride	Mechanism unknown	Inadequate supply in food and water
		Inadequate supplementation
Selenium	Component of glutathione peroxidase	Inadequate amounts in soil and water
	Antioxidant with vitamin E	



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Figure 8-23 The circuitry that regulates energy balance. When sufficient energy is stored in adipose tissue and the (insulin, leptin, ghrelin, peptide YY) are delivered to the central neuronal processing units, in the hypothalamus. H and activate catabolic circuits. The effector arms of these central circuits then influence energy balance by inhibiting This in turn reduces the energy stores, and the adiposity signals are blunted. Conversely, when energy stores are low, the hypothalamus activates anabolic circuits to generate energy stores in the form of adipose tissue, thus c

By mechanisms not clearly understood, the *output of leptin is regulated by the adequacy of fat stores*. When fat stores are low, leptin secretion is stimulated, and the hormone travels to the hypothalamus, where it binds to leptin receptors. This class of leptin-sensitive neurons produces the feeding-inducing (*orexigenic*) neuropeptides, neuropeptide Y (NPY) and agouti-related protein (AgRP). The other class of leptin receptor-bearing neurons produces *anorexigenic* peptides (pro-opiomelanocortin [POMC] and cocaine- and amphetamine-related transcript [CART]). The actions of the orexigenic and anorexigenic peptides are mediated by binding to another set of receptors, the two most important being the NPY receptor and the melanocortin-4 receptor (MC4R). *Leptin binding reduces food intake by stimulating the production of anorexigenic peptides and inhibiting the synthesis of NPY and AgRP (orexigenic peptides)*. The opposite sequence of events occurs in the case of inadequate stores of body fat: leptin secretion is diminished and food intake is increased. In individuals with obesity, leptin secretion is increased, but the hypothalamus fails to respond appropriately, leading to continued overeating and weight gain.

inadequate stores of body fat, leptin secretion is diminished and food intake is increased. In many of these pathways are balanced.

As indicated earlier, leptin regulates not only energy intake (appetite) but also energy expenditure. The abundance of leptin increases physical activity, production of heat, and energy expenditure. The mechanisms of energy expenditure are less well defined. *Thermogenesis* is probably the most important of the mechanisms in the hypothalamus. Thermogenesis seems to be controlled in part by hypothalamic signals that innervate sympathetic nerve endings in adipose tissue. Fat cells express  $\beta_3$ -adrenergic receptors that, when activated, promote fatty acid hydrolysis and also uncouple energy production from storage.

In rodents and humans, mutations that affect the central melanocortin circuit give rise to massive obesity. In mice, if the leptin gene or its receptor continue to eat and gain weight. These mice fail to sense the adequacy of food intake as if they are undernourished. As in mice, mutations of the leptin gene or receptor cause massive obesity in humans. Patients are rare. More commonly, mutations of the MC4R gene give rise to obesity, as is the case with *leptin receptor* mutations. While these monogenic forms of human obesity are uncommon, they underscore the importance of the control of body weight. Furthermore, they suggest that other acquired defects in these pathways are common forms of obesity. For example, in many obese individuals, blood leptin levels are high, suggesting that leptin deficiency may be more prevalent in humans.

There is little doubt but that genetic influences play an important role in weight control. However, obesity is not merely a genetic disease. There are definite environmental influences; the prevalence of obesity in the United States is much higher than in those who remain in their native land. These changes in all likelihood reflect changes in the amount of dietary intake. After all, regardless of genetic makeup, obesity would not occur without excess food intake.

### *Consequences of Obesity*

Obesity, particularly central obesity, increases the risk for a number of conditions, including diabetes mellitus and is associated with low HDL cholesterol (Chapter 10), which are major risk factors for coronary artery disease. The underlying mechanisms of these associations are complex and probably interrelated. Obesity, for instance, is associated with hyperinsulinemia, important features of type 2 diabetes (formerly known as non-insulin-dependent diabetes mellitus) with improvement (Chapter 20). It has been speculated that excess insulin, in turn, may play a role in the development of hypertension, production of excess norepinephrine, and smooth muscle proliferation that are the underlying mechanisms of hypertension. The risk of developing hypertension among previously normotensive persons increases with obesity.

Obese persons are likely to have hypertriglyceridemia and a low HDL cholesterol value, and these abnormalities are associated with coronary artery disease in the very obese. It should be emphasized that the association between obesity and coronary artery disease is not straightforward, and such linkage as there may be relates more to the associated diabetes and hypertension. Obesity, dyslipidemia, hypertension, and insulin resistance are components of a condition known as the metabolic syndrome, which predisposes to cardiovascular disease and type 2 diabetes. Adipose tissue plays a role in the pathogenesis of the metabolic syndrome, source of leptin, pro-inflammatory molecules such as TNF and IL-6, and anti-inflammatory agents.

*Nonalcoholic steatohepatitis* is commonly associated with obesity and type 2 diabetes. This condition, a liver disease, can progress to fibrosis and cirrhosis.

*Cholelithiasis (gallstones)* is six times more common in obese than in lean subjects. The mechanism involves increased cholesterol, increased cholesterol turnover, and augmented biliary excretion of cholesterol in the bile, leading to the formation of cholesterol-rich gallstones (Chapter 16).

*Hypoventilation syndrome* is a constellation of respiratory abnormalities in very obese persons. It is characterized by *hypoventilation syndrome*, after the fat lad who was constantly falling asleep in Charles Dickens' *Pickwick Papers* during the day, is characteristic and is often associated with apneic pauses during sleep, polycythemia, and cor pulmonale.

Marked adiposity predisposes to the development of degenerative joint disease (*osteoarthritis*). This disease, which appears in older persons, is attributed in large part to the cumulative effects of wear and tear on joints with the greater the trauma to joints with passage of time.

Obesity increases the risk of *ischemic stroke*, but the relationship between *obesity and stroke* is unclear in the literature. According to some, the true relationship is between stroke and hypertension, not obese patients who are not hypertensive are not at higher risk for stroke).

Equally controversial is the relationship between *obesity and cancer*, particularly cancers arising in the gastrointestinal tract. This problem is complicated by the role of particular foods, such as animal fats, which may be independent of obesity. Nevertheless, it has been estimated that overweight and obesity may be associated with an increased risk of cancer in women and 14% of deaths in men. Obese women are at a higher risk of developing endometrial cancer. This relationship may be indirect; high estrogen levels are associated with increased risk of cancer, and obesity is known to raise estrogen levels. With breast cancer the data are controversial. It seems that women who live in countries with a moderate or low risk of breast cancer (e.g., Japan), central obesity is associated with an increased risk of cancer. Again, the role of sex hormones is a confounding variable.

### SUMMARY

**Obesity** Obesity is a disorder of energy regulation. It increases the risk for a number of conditions such as insulin resistance, type 2 diabetes, hypertension, and hyperlipidemia, which are associated with the development of coronary artery disease. The regulation of energy balance is very complex. It has three main components: (1) afferent signals provided by the gut, including ghrelin and PYY; (2) the central hypothalamic melanocortin system, which integrates these signals and triggers the efferent signals; and (3) efferent signals that control energy expenditure. A key role in energy balance is played by adipose tissues. Its output from adipose tissues is regulated by leptin. Leptin binding to its receptors in the hypothalamus reduces food intake and stimulates anorexigenic peptides and inhibiting the synthesis of orexigenic peptides. Obesity is also associated with the development of nonalcoholic fatty liver disease, which may progress to fibrosis and cirrhosis. Obesity increases the formation of cholesterol gallstones. Obesity is associated with an increased risk of endometrial and breast cancers, perhaps as a result of hormonal changes.

### Diet and Systemic Diseases

The problems of under- and overnutrition, as well as specific nutrient deficiencies, have been discussed. However, even in the absence of any of these problems, diet may make a significant contribution to the causation of many diseases. A few examples suffice here.

Currently, one of the most important and controversial issues is the contribution of diet to atherosclerosis. Dietary modification—specifically, reduction in the consumption of cholesterol and saturated animal fats—can reduce serum cholesterol levels and prevent or retard the development of atherosclerosis (most important in the elderly). The average adult in the United States consumes a large amount of fat and cholesterol daily, with a ratio of saturated to polyunsaturated fatty acids of about 3 : 1. Lowering the level of saturates to the level of the polyunsaturates can reduce serum cholesterol level within a few weeks. Vegetable oils (e.g., corn and safflower oil) are rich in polyunsaturated fatty acids and are good sources of such cholesterol-lowering lipids. Fish oil fatty acids, which have more double bonds than do the omega-6, or n-6, fatty acids found in vegetable oils. A study of Dutch men showed that consumption of fish revealed a substantially lower frequency of death from coronary heart disease than that of a control group. Dietary modification can affect heart disease, currently there are insufficient data to suggest that consumption of omega-3 fatty acids is of benefit in reducing coronary artery disease.

There are other examples of the effect of diet on disease.

Hypertension is beneficially affected by restricting sodium intake. Dietary fiber, or roughage, is thought by some to have a preventive effect against diverticulosis of the colon. Caloric restriction has been demonstrated to increase life span in experimental animals. The basis of this striking observation is unclear. Garlic has been touted to protect against heart disease (and also, alas, against kisses—and to prove this effect unequivocally).

### Diet and Cancer



With respect to carcinogenesis, three aspects of the diet are of concern: (1) the content of exogenous substances, (2) the synthesis of carcinogens from dietary components, and (3) the lack of protective factors.

Regarding *exogenous* substances, *aflatoxin* is clearly carcinogenic, and constitutes an important cause of hepatocellular carcinomas in parts of Asia and Africa. Exposure to aflatoxin causes a specific mutation in tumor cells. The presence of the mutation can be used as a molecular signature for aflatoxin exposure. Debate continues about the carcinogenicity of food additives, artificial sweeteners, and color additives. Artificial sweeteners (cyclamates and saccharin) have been implicated in bladder cancers, but controversy exists about *endogenous* synthesis of carcinogens or promoters from components of the diet related to nitrosamines. *Nitrosamines and nitrosamides* are implicated in the generation of these tumors in humans and in the induction of gastric cancer in animals. These compounds can be formed in the body from nitrosamines and nitrites. Sources of nitrites include sodium nitrite added to foods as a preservative and in cured meats, and vegetables, which are reduced in the gut by bacterial flora. There is, then, the potential for nitrosamines to be formed from dietary components, which might well have an effect on the stomach. High animal protein intake has been implicated in the causation of colon cancer. The most convincing explanation for the effect of fat intake increases the level of bile acids in the gut, which in turn modifies intestinal flora, and increases the number of bacteria. The bile acids or bile acid metabolites produced by these bacteria might serve as promoters. The effect of a high-fiber diet might relate to (1) increased stool bulk and decreased transit time, which dilutes putative offenders, and (2) the capacity of certain fibers to bind carcinogens and promoters. Documenting these theories in clinical and experimental studies have, on the whole, led to controversy. Antioxidants, carotenenes, and selenium have been assumed to have anticarcinogenic effects because of their antioxidant properties. To date there is no convincing evidence that these antioxidants act as chemopreventive agents. Vitamin A promotes epithelial differentiation and is believed to reverse squamous metaplasia. Better results have been seen with therapy in promyelocytic leukemia, as discussed earlier in this chapter.

Thus, we must conclude that despite many tantalizing trends and proclamations by "diet gurus," the general conclusion is that diet can cause or protect against cancer. Nonetheless, concern persists that carcinogens lurk in our food and in rich ice cream.

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## 9 General Pathology of Infectious Diseases\*

In many ways infectious diseases are as important to human history as wars and natural disasters; consider the Black Death of the Middle Ages, the wholesale death of Native Americans from measles and smallpox (many more than from bullets and starvation), or acquired immunodeficiency syndrome (AIDS). Infectious disease is also an important driving force in vertebrate evolution, underlying the development and progressive complexity of the human immune system. Despite medical advances, we have actually defeated only a handful of these diseases; notably, almost all the victories are due to immunization programs (e.g., smallpox, whooping cough, polio, and measles) that succeed by augmenting our own immunity. Although antibiotic usage has indeed contributed to the taming of some infectious diseases, indiscriminate use also has resulted, ironically, in the development of increasingly virulent, multiple drug-resistant pathogens. As a result, microbes once easily controlled have come roaring back: resistant strains of tuberculosis, malaria, salmonella, gonorrhea, and even the lowly streptococci.

Thus, infectious diseases remain important causes of death around the globe. In developing countries, unsanitary living conditions and malnutrition contribute to a massive burden of infectious disease responsible for more than 10 million deaths annually; most occur in children, especially from respiratory and diarrheal infections. Even in the United States, two of the top 10 leading causes of death are attributable to infection (pneumonia and sepsis). Infectious diseases are particularly important causes of death among the elderly and individuals with AIDS, as well as among those with chronic diseases. Medical advances like chemotherapy for tumors and immunosuppression for organ transplantation have also created a whole new class of patients vulnerable to usually innocuous but nevertheless *opportunistic* organisms.

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In the face of what seems to be an overwhelming onslaught of microbes, it is well to remember that *cooperation* between microorganisms and humans is the rule; disease is the exception. Indeed, without our normal gut flora, we would be at risk for vitamin K deficiency and the normal vaginal flora prevent recurrent *Candida* ("yeast") infections. The majority of these relationships are *symbiotic* (of benefit to both partners) or, at worst, *commensal* (the fellow passenger shares the host's food without causing harm). When microbes cause disease, the nature and extent of the pathology depend on (1) the *virulence* (or pathogenicity) of the microorganism and (2) the *response of the host*. Consequently, infection in the microbiologic sense is not synonymous with infectious disease in a clinical sense; *infectious disease* occurs when there is tissue injury or altered host physiology.

The goal of this chapter is to highlight the general mechanisms by which infectious organisms cause pathology. Only a few of the many human pathogens will be described to illustrate specific concepts of microbial pathogenesis. Greater coverage of most organisms can be found in the chapters focusing on individual organ systems.



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## HISTORY

An overview of the evolution of our knowledge about infectious diseases is not only interesting but also provides an important historical perspective to understanding the concepts of microbial pathogenesis. Microbiology, immunology, infectious disease, and even public health are very much interwoven throughout the story.

Edward Jenner noticed that milkmaids working with cows were resistant to smallpox. His seminal observation in 1796 (even without knowing the infectious agent!) eventually led to an understanding of cross-reactive immunity and immunization; we know now that the cowpox virus (*Vaccinia*) induces antibody responses that neutralize subsequent infection with the considerably more virulent smallpox virus (*Variola*). Seventy years later (in 1865), Louis Pasteur was the first to demonstrate that microorganisms can in fact cause disease (germ theory of disease); he also created the first attenuated vaccines, including one for rabies in 1885. In 1882 Robert Koch championed the criteria for connecting a specific microorganism to a disease. Koch's postulates (interestingly enough, first applied in linking the anthrax bacillus to its specific disease constellation) require that (1) a causal organism be found in disease lesions, (2) the organism be isolable in culture, (3) secondary inoculation of the purified organism causes lesions (usually in experimental animals), and (4) the organism be recoverable from the experimental animal.

Modern microbiology, based on molecular genetics, arrived in 1944, when Oswald Avery demonstrated that transfer of deoxyribonucleic acid (DNA) from virulent to avirulent *Streptococcus pneumoniae* transformed the latter into a virulent phenotype. This conclusively proved that DNA is the material responsible for transmission of genetic traits, and it was the starting point for the explosion of research in molecular genetics that continues to this day.

Improved techniques in cell and tissue culture led to additional advances in infectious disease; previously, viral propagation relied on passage through animal hosts, making manipulation and observation problematic. The successful culture of polioviruses in human fetal tissues and foreskin fibroblasts in roller bottles by Enders and Weller in 1949 led to the development of formalin-killed and, eventually, attenuated live vaccines. Much later, identification of the human immunodeficiency virus (HIV) by Montagnier and Gallo in 1984 led to the subsequent development of diagnostic tests for screening blood, and to antiviral therapies based on understanding the structure of particular HIV enzymes; the race is on worldwide to develop an effective vaccine. Today, the entire genomic sequences of many species, including microbes and humans, are known, and this holds great promise for future research into the pathogenesis, diagnosis, and treatment of infectious diseases.





## NEW AND EMERGING INFECTIOUS DISEASES

Some infectious diseases have coexisted with humans throughout our history; thus, leprosy has been known since at least biblical times, parasitic schistosomes have been found in Egyptian mummies, and many bacteria, fungi, and viruses probably plagued even prehistoric humans. Nevertheless, the arrival of new diseases has punctuated human history, and a surprising number of new infectious agents are described each year ([Table 9-1](#)). For example, venereal syphilis was unknown before the siege of Naples in 1494, Legionnaires' disease first appeared in 1976 in Philadelphia, Lyme disease first surfaced in the mid-1970s, AIDS was not recognized until the early 1980s, and "flesh-eating streptococci" are a recent popular staple of the tabloid press.

**Table 9-1. Some Recently Recognized Infectious Agents and the Diseases They Cause**

Year	Agent	Disease
1977	Ebola Virus	Epidemic hemorrhagic fever
	Hanta virus	Hemorrhagic fever with renal disease
	<i>Legionella pneumophila</i>	Legionnaires' disease
	<i>Campylobacter jejuni</i>	Enteritis
1981	<i>Staphylococcus aureus</i>	Toxic shock syndrome
1982	<i>Escherichia coli</i> O157 : H7	Hemolytic-uremic syndrome
	<i>Borrelia burgdorferi</i>	Lyme disease
1983	HIV	AIDS
	<i>Helicobacter pylori</i>	Gastric ulcers
1988	Hepatitis E	Enterically transmitted hepatitis
1989	Hepatitis C	Chronic hepatitis
1992	<i>Vibrio cholerae</i> O139	New epidemic cholera strain
	<i>Bartonella henselae</i>	Cat-scratch disease
1995	KSHV (HHV-8)	Kaposi sarcoma in AIDS
2002	West Nile virus	Acute flaccid paralysis
2003	SARS coronavirus	Severe acute respiratory syndrome

Adapted from Lederberg J: Infectious disease as an evolutionary paradigm. *Emerg Infect Dis* 3:417, 1997.

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The infectious causes of some "new" diseases (e.g., *Helicobacter* gastritis, hepatitis B and C, rotavirus diarrhea, and Legionnaires' pneumonia) were previously unrecognized, largely because the infectious agents were difficult to culture. Other infections may genuinely be new to humans (e.g., HIV causing AIDS, *Borrelia burgdorferi* causing Lyme disease, and new exotic strains of *influenza*). Such apparently new entities probably arise from microbial mutations and/or recombinations among different organisms that alter their virulence factors or change their host specificity. Certain "new" disease entities are also being recognized only because of an expanding cohort of immunocompromised hosts (e.g., cytomegalovirus [CMV], Kaposi sarcoma herpesvirus [KSHV, or HHV-8], *Mycobacterium avium-intracellulare*, *Pneumocystis jiroveci* [carinii], and *Cryptosporidium parvum*). Changes in the environment may increase the rates of other infectious diseases: reforestation of the eastern part of the United States led to massive increases in deer and mice carrying the ticks that transmit Lyme disease, babesiosis, and ehrlichiosis. Finally, as mentioned above, the emergence of multiple drug-resistant strains of *M. tuberculosis*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, and



*Enterococcus faecium* also represents a challenge to medicine.



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## AGENTS OF BIOTERRORISM

The "weaponization" of biologic agents as a terrorist strategy has long been a theoretical threat; it unfortunately became reality with the US anthrax attacks in 2001. The Centers for Disease Control and Prevention have evaluated the microorganisms that pose the greatest danger as weapons (based on efficiency of disease transmission, difficulty of microbial propagation and distribution, difficulty of defending against, and potential for inciting fear in the public), ranking them in three categories ([Table 9-2](#)).

**Table 9-2. Potential Agents of Bioterrorism**

Category A Diseases/Agents	Category B Diseases/Agents	Category C Diseases/Agents
Anthrax ( <i>Bacillus anthracis</i> ) Botulism ( <i>Clostridium botulinum</i> toxin) Plague ( <i>Yersinia pestis</i> ) Smallpox ( <i>Variola major</i> virus) Tularemia ( <i>Francisella tularensis</i> ) Viral hemorrhagic fevers: filoviruses (e.g., Ebola, Marburg), arenaviruses (Lassa fever virus and New World arenaviruses), bunyaviruses (e.g., Crimean-Congo hemorrhagic fever and Rift Valley Fever viruses)	Brucellosis ( <i>Brucella</i> species) Epsilon toxin of <i>Clostridium perfringens</i> Food safety threats (e.g., <i>Salmonella</i> species, <i>Escherichia coli</i> O157 : H7, <i>Shigella</i> ) Glanders ( <i>Burkholderia mallei</i> ) Meliodosis ( <i>Burkholderia pseudomallei</i> ) Psittacosis ( <i>Chlamydia psittaci</i> ) Q fever ( <i>Coxiella burnetti</i> ) Ricin toxin from <i>Ricinus communis</i> (castor beans) Staphylococcal enterotoxin B Typhus fever ( <i>Rickettsia prowazekii</i> ) Viral encephalitis: alphaviruses (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis) Water safety threats (e.g., <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i> )	Emerging infectious disease threats such as Nipah virus and Hantavirus

Adapted from Centers for Disease Control and Prevention information.

Category A agents are the highest risk agents, with easy dissemination and high potential for mortality, thus posing the greatest public panic and social disruption. Smallpox falls in this category because of its high transmissibility (respiratory aerosol or direct contact with skin lesions), low required infective dose, mortality rate of 30%, and lack of effective antiviral therapy. Since the United States stopped vaccinating for smallpox in 1972, with a subsequent drop in general immunity, the total population is highly susceptible. Category B agents are relatively easy to disseminate and produce moderate morbidity but low mortality (except in immune-compromised populations); many of these agents are food- or waterborne. Category C agents include emerging pathogens that have the potential for mass dissemination and high morbidity and mortality.





## CATEGORIES OF INFECTIOUS AGENTS

Agents that cause infectious diseases range in size from the 27-kD prion protein to the 20-nm poliovirus. The following brief descriptions of the categories of infectious agents are not intended to be all-inclusive concepts.

### Prions

Prions are abnormal forms of a normal host *prion protein* (PrP) found in high levels in neurons; the name derives from proteinaceous infectious particles) cause transmissible spongiform encephalopathies (human cannibalism), Creutzfeldt-Jakob disease (CJD; associated with corneal transplants, among others), variant Creutzfeldt-Jakob disease (vCJD; associated with BSE), and bovine spongiform encephalopathy (BSE; popularly known as "mad cow disease"), and variant Creutzfeldt-Jakob disease (vCJD; associated with BSE-infected cattle). The spongiform encephalopathies occur when a PrP undergoes a conformational change and acquires protease resistance. The protease-resistant PrP then promotes conversion of the normal protease-sensitive PrP into the protease-resistant form, explaining the "infectious" nature of these diseases. Accumulation of abnormal PrP leads to neurodegeneration and "spongiform" changes in the brain. Spontaneous or inherited PrP mutations that make PrP intrinsically more stable are observed in the sporadic and familial forms of CJD, respectively. These diseases are discussed in

Table 9-3. Classes of Human Pathogens and Their Habitats

Taxonomic	Size	Site of Propagation	Sample Species
Prions	Proteins	Intracellular	PrP
Viruses	20-300 nm	Obligate intracellular	Poliovirus
Chlamydiae	200-1000 nm	Obligate intracellular	<i>Chlamydia trachomatis</i>
Rickettsiae	300-1200 nm	Obligate intracellular	<i>Rickettsia prowazekii</i>
Mycoplasmas	125-350 nm	Extracellular	<i>Mycoplasma pneumoniae</i>
Bacteria	0.8-15 µm	Cutaneous	<i>Staphylococcus aureus</i>
		Mucosal	<i>Vibrio cholerae</i>
		Extracellular	<i>Streptococcus pneumoniae</i>
		Facultative intracellular	<i>Mycobacterium tuberculosis</i>
		Facultative intracellular	<i>Mycobacterium tuberculosis</i>
Fungi	2-200 µm	Cutaneous	<i>Trichophyton</i> sp.
		Mucosal	<i>Candida albicans</i>
		Extracellular	<i>Sporothrix schenckii</i>
		Facultative intracellular	<i>Histoplasma capsulatum</i>
Protozoa	1-50 µm	Mucosal	<i>Giardia lamblia</i>
		Extracellular	<i>Trypanosoma gambiense</i>
		Facultative intracellular	<i>Trypanosoma cruzi</i>
		Obligate intracellular	<i>Leishmania donovani</i>
Helminths	3 mm-10 m	Mucosal	<i>Enterobius vermicularis</i>
		Extracellular	<i>Wuchereria bancrofti</i>
		Intracellular	<i>Trichinella spiralis</i>

### Viruses

Viruses are obligate intracellular organisms that commandeer the host cell's biosynthetic and replicative machinery. They consist of a nucleic acid genome surrounded by a protein coat (called a capsid) and, occasionally, a lipid envelope. Viruses may be classified by some combination of their nucleic acid genome (DNA or ribonucleic acid), the shape of the capsid (icosahedral or helical), the presence or absence of a lipid envelope, the mode of replication (obligate intracellular or facultative intracellular), the type of pathology they cause (Table 9-4), or the type of pathology they cause (Table 9-4).

Because viruses are individually smaller than the limits of light microscopic resolution (20-300 nm electron microscopy). However, certain viruses have the propensity to aggregate within the cells to form *inclusion bodies*; these may be visualized by light microscopy and may be diagnostically helpful. Thus, CMV (hence the prefix *cytomegalo*-) and have characteristic inclusion bodies-both eosinophilic nuclear and cytoplasmic inclusions (Fig. 9-1A). In comparison, herpesviruses can form a large nuclear inclusion and in chronic hepatitis B virus (HBV) infections, accumulated hepatitis B surface antigen (HBsAg) in hepatocytes (Fig. 9-1C). It should, however, be emphasized that most viruses do not give rise to

**Table 9-4. Selected Human Viral Diseases**

<b>Viral Pathogen</b>	<b>Disease Expression</b>
<b>Respiratory</b>	
Adenovirus	Upper and lower respiratory tract infections, conjunctivitis, diarrhea
Rhinovirus	Upper respiratory tract infection
Influenza viruses A, B	Influenza
Respiratory syncytial virus	Bronchiolitis, pneumonia
<b>Digestive</b>	
Mumps virus	Mumps, pancreatitis, orchitis
Rotavirus	Childhood diarrhea
Hepatitis A-E virus	Acute and chronic hepatitis
<b>Systemic with Skin Eruptions</b>	
Measles virus	Measles (rubeola)
Varicella-zoster virus	Chickenpox, shingles
Herpes simplex virus 1	"Cold sore"
Herpes simplex virus 2	Genital herpes
<b>Systemic with Hematopoietic Disorders</b>	
Cytomegalovirus	Cytomegalic inclusion disease
Epstein-Barr virus	Infectious mononucleosis
HIV-1 and HIV-2	AIDS
<b>Arboviral and Hemorrhagic Fevers</b>	
Dengue virus 1-4	Dengue, hemorrhagic fever
Yellow fever virus	Yellow fever
<b>Warty Growths</b>	
Papillomavirus	Condyloma; cervical carcinoma
<b>Central Nervous System</b>	
Poliovirus	Poliomyelitis
JC virus	Progressive multifocal leukoencephalopathy (opportunistic)

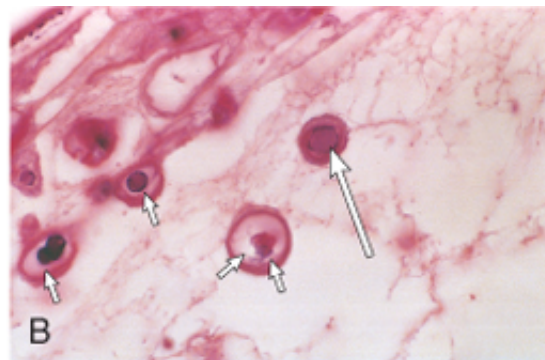
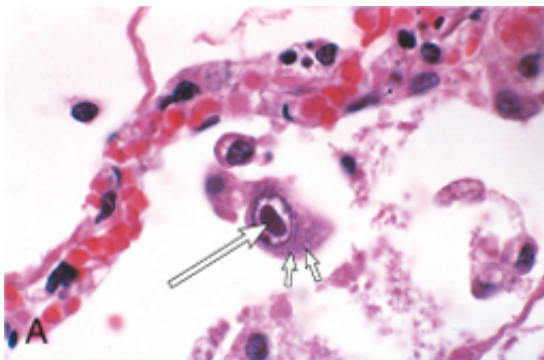


Figure 9-1 Examples of viral inclusions. **A**, Cytomegalovirus infection in the lung; infected cells show distinct nuclear and cytoplasmic inclusions. **B**, Mucosal herpesvirus infection; infected cells show glassy nuclear inclusions (long arrows). **C**, Hepatitis B viral infection in liver; in chronic infections, infected hepatocytes show diffuse granular (granular) cytoplasmic inclusions (short arrows) and hepatitis B surface antigen (HBsAg).

Viruses account for a large share of human infections. Different species of viruses can produce the same clinical manifestations (e.g., respiratory infection); conversely, a single virus can cause different clinical manifestations depending on the site of infection (e.g., CMV). While many viruses cause transient illnesses (e.g., the common cold and influenza), others cause chronic diseases (e.g., HIV, hepatitis B, hepatitis C, and hepatitis D). Some viruses, either continuing to multiply (e.g., chronic HBV) or surviving in some nonreplicating form within the host (e.g., herpesviruses), establish latency. Thus, the herpes varicella-zoster (chickenpox) virus, establishes latency in the dorsal root ganglia and can reactivate years later to cause shingles, an extremely painful cutaneous lesion. Some viruses also have the nasty capacity to transform normal cells into cancer cells (see below).

### *Bacteriophages, Plasmids, and Transposons*

These are mobile genetic elements that infect bacteria and can indirectly promulgate human disease by transferring genetic factors (e.g., adhesins, toxins, or enzymes). Exchange of these elements between bacteria often confers a selective advantage (e.g., antibiotic resistance), and/or converts otherwise nonpathogenic bacteria into virulent pathogens.

### *Bacteria*

Bacterial infections are common causes of disease (Table 9-5). Bacterial cells are prokaryotes: they lack a membrane-bound nucleus and other membrane-enclosed organelles. They are also bound by a cell wall, a polymer made up of a mixture of sugars and amino acids; many antibiotics function by inhibiting synthesis of the cell wall. Bacterial cell walls generally occur in one of two varieties: a thick wall surrounding the cell membrane (Gram-positive) or a thin cell wall sandwiched between two phospholipid bilayer membranes (these do not stain Gram-negative) (Fig. 9-2). Bacteria are classified by Gram staining (positive or negative), shape (cocci or bacilli), and form of respiration (aerobic or anaerobic) (Fig. 9-3). Many bacteria have flagella (see Fig. 9-2) that allow attachment to host cells. Most bacteria synthesize their own food, while some are obligate intracellular parasites. Most bacteria remain extracellular, while some can grow only within host cells. Others can survive and replicate either outside or inside of host cells (facultative intracellular bacteria).

Normal healthy people are colonized by as many as  $10^{10}$  bacteria in the mouth,  $10^{12}$  bacteria on the gastrointestinal (GI) tract. Aerobic and anaerobic bacteria in the mouth, particularly *Streptococcus* and *Lactobacillus*, are the major cause of tooth decay. Bacteria colonizing the skin include *Staphylococcus epidermidis* and *Propionibacterium acnes*. In the colon, 99.9% of bacteria are anaerobic.

### *Chlamydiae, Rickettsias, and Mycoplasmas*

Like bacteria, these organisms divide by binary fission and are sensitive to antibiotics. However, they lack certain structures (e.g., *Mycoplasma* lack a cell wall) or metabolic capabilities (e.g., they lack adenosine triphosphate [ATP]) that distinguish them from bacteria. *Chlamydia* and *Rickettsia* species that replicate in membrane-bound vacuoles in epithelial cells and the cytoplasm of endothelial cells for their transmission by arthropod vectors, including lice, ticks, and mites.

*Chlamydia trachomatis* is the most frequent infectious cause of female sterility (by scarring fallopian tubes) and conjunctival inflammation that eventually scars and opacifies the cornea. By injuring endothelial cells, it causes vasculitis (often presenting as a rash), but they can also cause pneumonia or hepatitis (Q fever) or cause death (Rocky Mountain spotted fever). *Mycoplasma* and the closely related genus *Ureaplasma* are also known; *M. pneumoniae* spreads from person to person by aerosols, binds to the surface of epithelial cells, and causes atypical pneumonia characterized by peribronchiolar infiltrates of lymphocytes and plasma cells (Chapter 18). *Ureaplasma* is transmitted venereally and may cause nongonococcal urethritis (Chapter 18).

### *Fungi*

**Table 9-5. Examples of Bacterial, Spirochetal, and Mycobacterial Disease**



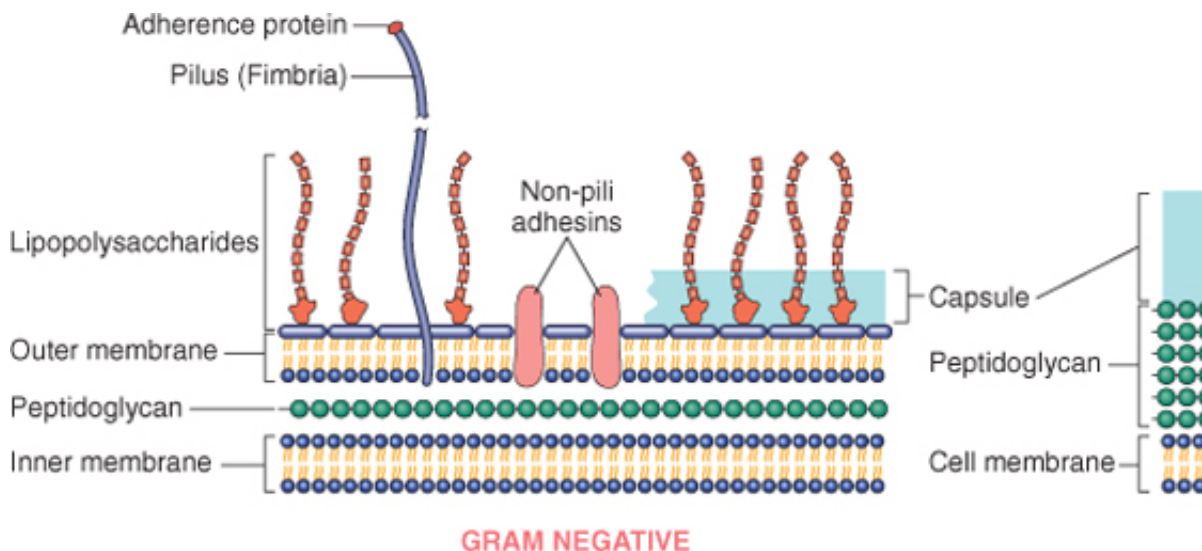
Clinical or Microbiologic Category	Species	Frequency
Infections by pyogenic cocci	<i>Staphylococcus aureus</i> , <i>S. epidermidis</i>	Abscesses
	<i>Streptococcus pyogenes</i> , $\beta$ -hemolytic	Upper respiratory tract infections, scarlet fever
	<i>Streptococcus pneumoniae</i> (pneumococcus)	Lobar pneumonia
	<i>Neisseria meningitidis</i> (meningococcus)	Cerebral meningitis
	<i>Neisseria gonorrhoeae</i> (gonococcus)	Gonorrhea
Gram-negative infections, common	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter (Aerobacter) aerogenes</i> , <i>Proteus</i> spp. ( <i>P. mirabilis</i> , <i>P. morgani</i> ) <i>Serratia marcescens</i> , <i>Pseudomonas</i> spp. ( <i>P. aeruginosa</i> )	Urinary tract infections, abscesses, endocarditis
	<i>Legionella</i> spp. ( <i>L. pneumophila</i> )	Legionnaires' disease
Contagious and childhood bacterial diseases	<i>Haemophilus influenzae</i>	Meningitis, infections
	<i>Bordetella pertussis</i>	Whooping cough
	<i>Corynebacterium diphtheriae</i>	Diphtheria
Enteropathic infections	Enteropathogenic <i>E. coli</i> , <i>Shigella</i> spp., <i>Vibrio cholerae</i> , <i>Campylobacter fetus</i> , <i>C. jejuni</i> , <i>Yersinia enterocolitica</i>	Invasive, sometimes fatal
	<i>Salmonella typhi</i>	Typhoid fever
Clostridial infections	<i>Clostridium tetani</i>	Tetanus
	<i>Clostridium botulinum</i>	Botulism
	<i>Clostridium perfringens</i> , <i>C. septicum</i>	Gas gangrene
	<i>Clostridium difficile</i>	Pseudomembranous colitis
Zoonotic bacterial infections	<i>Bacillus anthracis</i>	Anthrax
	<i>Yersinia pestis</i>	Bubonic plague
	<i>Francisella tularensis</i>	Tularemia
	<i>Brucella melitensis</i> , <i>B. suis</i> , <i>B. abortus</i>	Brucellosis
	<i>Borrelia recurrentis</i>	Relapsing fever
	<i>Borrelia burgdorferi</i>	Lyme disease
Human treponemal infections	<i>Treponema pallidum</i>	Syphilis
Mycobacterial infections	<i>Mycobacterium tuberculosis</i> , <i>M. bovis</i>	Tuberculosis
	<i>M. leprae</i>	Leprosy
Actinomycetaceae	<i>Nocardia asteroides</i>	Nocardiosis
	<i>Actinomyces israelii</i>	Actinomycetosis

Fungi are eukaryotes possessing thick chitin-containing cell walls and ergosterol-containing cell membrane constituents are the targets of most antifungal agents. Fungi can grow either as budding yeasts or as filamentous hyphae. Hyphae may be septate (cell walls separate individual cells) or aseptate, a distinction important in identifying fungi. Some pathogenic fungi show *thermal dimorphism*; that is, they grow as hyphae at room temperature but produce spores sexually or, more commonly, asexual spores (*conidia*); the latter are produced on arising along hyphal filaments.

Fungi may cause superficial or deep infections. Superficial infections typically involve the skin, hair, and nails. Fungal species confined to superficial skin layers; these infections are commonly referred to by the name of the fungus (e.g., "ringworm") followed by the area of the body affected (tinea pedis is "athlete's foot," while tinea capitis is "scalp ringworm"). Deep infections are caused by species that invade the subcutaneous tissue, causing abscesses or granulomas (e.g., sporotrichosis and cryptococcosis). In most cases, these infections usually heal or remain latent in normal hosts; in immunocompromised hosts, however, they can become life-threatening.

tissues, destroying vital organs. Some species responsible for deep fungal infections are limited to *Coccidioides* in the American Southwest and *Histoplasma* in the Ohio River Valley). By contrast, in immunocompromised hosts (opportunistic fungi such as *Candida*, *Aspergillus*, *Mucor*, and *Cryptococcus*), these fungi can invade normal human epithelia without causing illness. In immunocompromised individuals these opportunistic infections are characterized by tissue necrosis, hemorrhage, and vascular occlusion. AIDS patients are particularly susceptible to opportunistic fungus *Pneumocystis jirovecii* (formerly called *P. carinii*).

### Protozoa

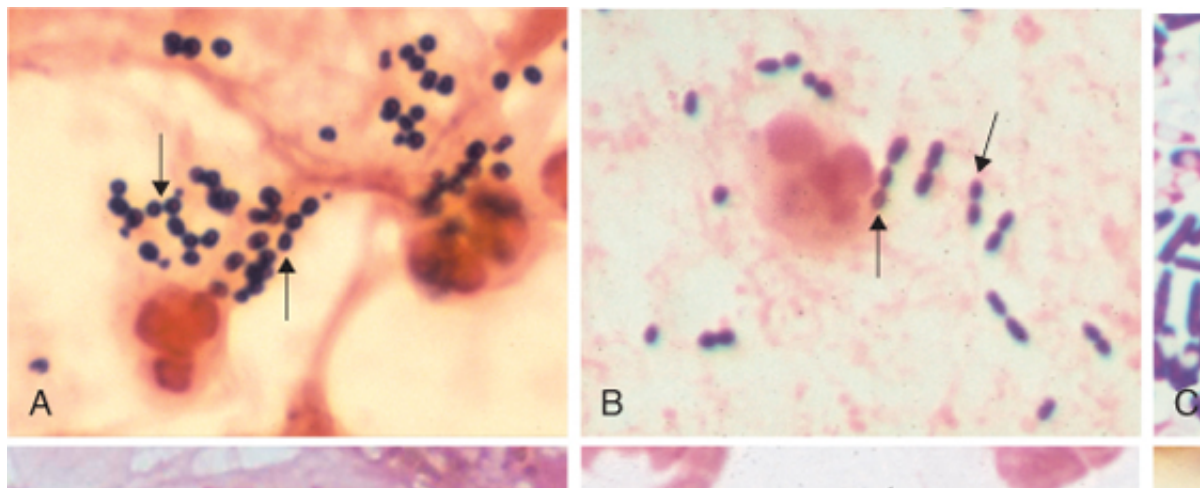


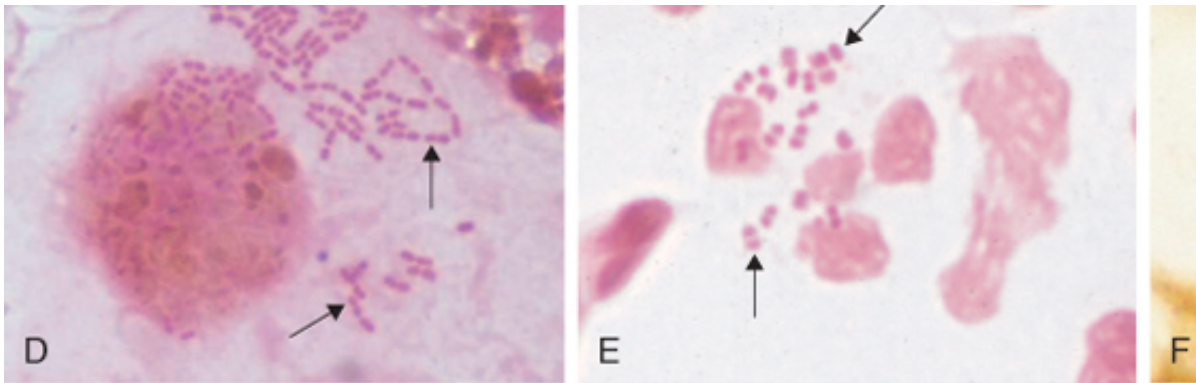
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Figure 9-2 Wall structure of gram-negative and gram-positive bacteria, including several of the surface molecule

Protozoa, single-celled eukaryotes, are among the major causes of morbidity and mortality in developing countries. They can replicate intracellularly in many cell types (e.g., malaria in erythrocytes, *Leishmania* in macrophages, *Trichomonas vaginalis* in the genital system, intestine, or blood). *Trichomonas vaginalis* is a sexually transmitted protozoan that can cause vaginitis. Most prevalent intestinal protozoans, *Entamoeba histolytica* and *Giardia lamblia*, have two forms: (1) non-motile trophozoites that multiply in the intestine and are infectious when ingested, and (2) motile trophozoites that multiply in the small intestine (e.g., *Plasmodium*, *Trypanosoma*, and *Leishmania*). *Toxoplasma gondii* is acquired either by contact with oocyst-shedding kittens or by consumption of cyst-ridden

### Helminths





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 Figure 9-3 Bacterial morphology. **A**, Gram stain of sputum from a patient with *Staphylococcus aureus* pneumonia among degenerating neutrophils. **B**, Gram stain of sputum from a patient with *Streptococcus pneumoniae* pneumonia showing pairs and short chains (arrows). **C**, Gram stain of cultured *Clostridium sordellii* showing a mixture of gram-positive spores (clear areas). **D**, Gram stain of a bronchoalveolar lavage specimen showing gram-negative intracellular bacteria (*Escherichia coli*). **E**, Gram stain of urethral discharge from a patient with *Neisseria gonorrhoeae* showing many gram-negative diplococci. **F**, Gram stain of brain tissue from a patient with Lyme disease meningoencephalitis; two helical spirochetes (*Borrelia burgdorferi*) are visible.

Parasitic worms are highly differentiated multicellular organisms with complex life cycles; most adult worms require a definitive host and asexual multiplication in an intermediary host or vector. Thus, depending on the worms (e.g., *Ascaris lumbricoides*), immature forms (e.g., *Toxocara canis*), or asexual larval forms (e.g., adult worms take up residence in humans, they generate eggs or larvae destined for the next phase of the life cycle). The clinical significance of a helminthic disease is usually proportionate to the number of infecting organisms (e.g., 10 hookworms cause severe anemia by consuming 100 mL of blood per day). Moreover, pathology results from inflammatory responses to the eggs or larvae rather than to the adult forms (e.g., the robust response in schistosomiasis). *Strongyloides stercoralis* is an exception in that larvae can become infectious in autoinfection in immunocompromised hosts.

Helminths comprise three classes:

**Roundworms (nematodes)** have a collagenous tegument and a nonsegmented structure. They include the hookworms, and *Strongyloides* species among the intestinal worms and the filariae and *Trichinella* invaders. **Flatworms (cestodes)** are gutless worms whose head (scolex) sprouts a ribbon of absorptive tegument. They include the pork, beef, and fish tapeworms and the cystic tapeworms. **Flukes (trematodes)** are primitive, leaflike worms with a syncytial integument; these include the blood-dwelling schistosomes.

### Ectoparasites

Ectoparasites are insects (lice, bedbugs, fleas) or arachnids (mites, ticks, spiders) that attach to a host and produce disease by direct tissue damage or indirectly by serving as the vectors for transmission of pathogens (e.g., transmit the Lyme disease spirochete *B. burgdorferi*). Some arthropods induce itching and excoriation (e.g., attached to hair shafts, or scabies caused by mites burrowing into the stratum corneum); at the site of attachment, there is associated with a mixed inflammatory infiltrate.





## TRANSMISSION OF MICROBES

The outcome of infection depends on the ability of a microbe to breach host barriers and colonize the host, and the ability of host defenses to eradicate the invader. *Host barriers to infection prevent microbes from establishing infection, and adaptive immune defenses* (see [Chapter 5](#)). Innate immunity is typically the first line of defense; it includes physical barriers to infection, phagocytic and natural killer (NK) cell mediators (e.g., cytokines, collectins, acute-phase reactants). Adaptive immune responses—mediators and products—are stimulated by microbial exposure and typically improve with successive contacts ([Chapter 6](#)).

### Routes of Infection

Microbes can enter the host by inhalation, ingestion, sexual transmission, insect or animal bites, or through breaks in intact host skin and mucosal surfaces and their secretory products (e.g., lysozyme in tears and saliva, and antibodies in breast milk). These are formidable defenses against most infections; for example, only four of every 10<sup>11</sup> *Vibrio cholerae* are required to produce vibrios cholera in human volunteers with normal gastric acid (having greater *virulence*) are able to overcome these barriers; thus, 100 *Shigella* organisms, *Giardia lamblia*, can be sufficient to cause disease. In general, in healthy individuals, respiratory, GI, or genitourinary infections are caused by less virulent organisms entering the skin through damaged sites (e.g., cuts, abrasions, insect bites). We describe the common routes of entry of microbes, host barriers to infections, and some of the ways in which microbes overcome these barriers.

#### Skin

The dense, keratinized outer layer of skin is a natural barrier to infection; its low pH (about 5.5) and its flora (including bacteria and fungi) are different from the normal bacterial and fungal flora adapted to that environment (including *Pseudomonas aeruginosa* and *Candida albicans*). Moreover, the keratinized outer layer is constantly shed and renewed so that it remains an effective barrier.

Although skin is usually an effective barrier, dermatophytes can infect the stratum corneum, hair, and nails. *Schistosoma* larvae released from freshwater snails can penetrate the skin, releasing collagenase, elastase, and other enzymes that dissolve the extracellular matrix. Superficial infections of the epidermis by *S. aureus* (impetigo) or by cutaneous fungi are all aggravated by heat and humidity. *Treponema pallidum* (agent of syphilis) both penetrates warm, moist skin and can cause venereal warts.

Most other microorganisms penetrate through breaks in the skin, including superficial cuts or abrasions (staphylococci), burns (*Pseudomonas aeruginosa*), and diabetic and pressure-related foot sores (bacteria). Catheters in hospitalized patients frequently cause bacteremia with *Staphylococcus* species or gram-negative bacteria. Whether deliberate (by needle-sharing drug abusers) or unintentional (accidental sticks by health care workers), these can transmit potentially infected blood and may transmit hepatitis B or C, or HIV. Bites by fleas, ticks, mosquitoes, and other insects transmit diverse infectious organisms, including arboviruses (causes of yellow fever and encephalitis), protozoans (malaria), and helminths (filariasis). Animal bites can lead to infections with bacteria or viruses.

#### Respiratory Tract

Some 10,000 microorganisms, including viruses, bacteria, and fungi, are inhaled daily by every citizen. The number of microorganisms that travel into the respiratory system is inversely proportional to their size. Large microorganisms are trapped in the upper respiratory tract in a mucus layer secreted by goblet cells; from there they are transported to the back of the throat, where they are swallowed and cleared. Organisms smaller than 5 μm reach the alveoli, where they are phagocytosed by alveolar macrophages or by neutrophils recruited to the site of infection.

The mucociliary clearance mechanism can be damaged by smoking (causing metaplasia of the nasal mucosa) or can be severely impeded by the hyperviscous mucus in cystic fibrosis. Intubation or gastric surgery can also damage the mucociliary clearance. However, in normal hosts, virulent respiratory pathogens succeed in establishing infection.

specifically adhering to respiratory epithelium. For example, influenza viruses express hemagglutinin residues on cell surface glycoproteins; once internalized, co-expressed viral neuraminidase releases the virus. Neuraminidase also lowers the viscosity of mucus and facilitates viral transit in the respiratory tract. Some organisms (e.g., *Haemophilus influenzae* or *Bordetella pertussis*) elaborate toxins that directly paralyze epithelial cells, also allowing *secondary infection* by organisms that normally lack the necessary adhesion (e.g., *Staphylococcus* species).

*M. tuberculosis* causes respiratory infections because it is able to escape phagocytotic killing by alveolar macrophages. Opportunistic fungi infect the lungs when cellular immunity is depressed or when leukocytes are depleted (e.g., AIDS patients and *Aspergillus* species in patients receiving chemotherapy).

### Intestinal Tract

Most GI pathogens are transmitted by food or drink contaminated with fecal material. Where hygiene is poor, transmission is rampant.

Normal defenses against ingested pathogens include (1) acidic gastric pH, (2) viscous mucus secreted by goblet cells, (3) bile detergents, (4) antimicrobial peptides called defensins, (5) immunoglobulin A (IgA) antibodies associated with mucosal lymphoid tissues, and (6) the normal gut flora. Pathogenic organisms must compete for space and nutrients with resident bacteria in the lower gut, and all gut microbes are also intermittently expelled by defecation.

Infections of the GI tract occur when local defenses are undermined or organisms develop strategies to evade defenses. Defenses are weakened by loss of gastric acidity, by antibiotics that unbalance the normal bacterial flora (e.g., *Clostridium difficile* colitis), or when there is stalled peristalsis or mechanical obstruction (e.g., in blind-loop syndrome).

Most enveloped viruses are killed by the bile and digestive enzymes, but nonenveloped viruses (e.g., rotaviruses, reoviruses, and Norwalk agents) are not.

Pathogenic bacteria in the GI tract cause disease by a variety of mechanisms:

Staphylococcal strains growing in contaminated food release powerful enterotoxins that cause food poisoning. *Vibrio cholerae* causes cholera by stimulating any bacterial multiplication in the gut. *Vibrio cholerae* and toxigenic *E. coli* multiply within the gut and cause the gut epithelium to secrete large volumes of watery diarrhea. *Shigella*, *Salmonella*, and *Campylobacter* invade the intestinal mucosa and lamina propria, causing ulceration, inflammation, and hemorrhagic dysentery. *Salmonella typhi* passes from the damaged mucosa through Peyer's patches into the bloodstream, resulting in a systemic infection.

Fungal infection of the GI tract occurs mainly in immunologically compromised hosts. *Candida albicans* infects the oral squamous epithelium, causing oral thrush or membranous esophagitis, but they may also disseminate to other systemic organs.

Intestinal protozoan infections particularly rely on cysts for transmission because they can resist harsh conditions. Motile trophozoites that attach to sugars on the intestinal epithelia via surface lectins. Other protozoa cross tissue barriers: *G. lamblia* attaches to the epithelial brush border, while *Cryptosporidium* organism and spores. *E. histolytica* causes contact-mediated cytolysis through a channel-forming pore protein in the colonic mucosa.

Intestinal helminthes such as *Ascaris* typically cause disease only when present in large numbers (e.g., causing intestinal obstruction or invading and damaging the bile ducts). Hookworms may cause iron deficiency anemia by feeding on intestinal villi. The fish tapeworm *Diphyllobothrium* can deplete its host of vitamin B<sub>12</sub>, giving rise to anemia. Finally, the larvae of several helminth parasites pass through the gut briefly on their way to other organs: larvae preferentially encyst in muscle, while *Echinococcus* larvae travel to the liver or lungs.

### Urogenital Tract

Even though urine can support the growth of many bacteria, the urinary tract is normally sterile because of the flow of urine. Successful pathogens (e.g., *E. coli*, gonococci) are those that can adhere to the epithelium. Women are more susceptible to urinary tract infections (UTIs) than men because the distance between the urinary bladder and the bacteria is shorter.

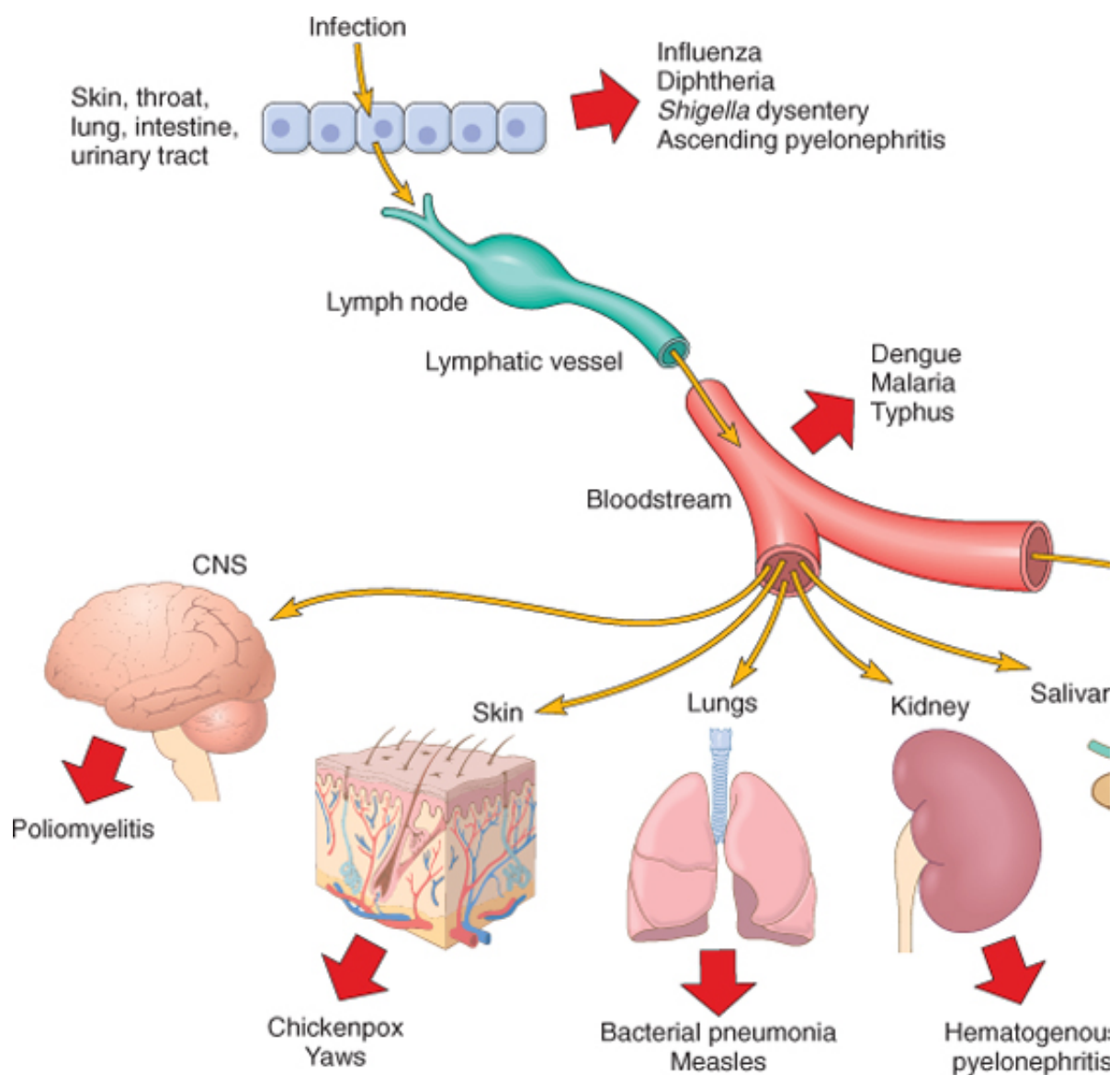


tract infections (UTIs) than men because the distance between the urinary bladder and the bacterium (urethra) is 5 cm in women, compared with 20 cm in men. Obstruction of urinary flow and/or reflux increases the risk of UTI. When a UTI spreads retrograde from the bladder into the kidney, it can cause acute pyelonephritis (Fig. 9-4).

From puberty until menopause, the vagina is protected from pathogens (mostly yeasts) by a low pH in the normal epithelium by commensal lactobacilli. Antibiotics can kill the lactobacilli and make them successful as pathogens; microorganisms have developed specific mechanisms for attaching to and invading via local breaks in the mucosa during sexual intercourse (genital warts, syphilis).

### Dissemination of Microbes Within the Body

Some microorganisms proliferate only locally at the site of infection, staying confined to the lumen or proliferate exclusively in or on epithelial cells (e.g., papillomaviruses, dermatophytes); others break out to other sites via the lymphatics, blood, or nerves (Fig. 9-4).



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Figure 9-4 Entry and dissemination of microbes. (Adapted from Mims CA: The Pathogenesis of Infectious D

A variety of pathogenic bacteria, fungi, and helminths are invasive by virtue of their motility or ability (e.g., staphylococci secrete **hyaluronidase** that degrades the extracellular matrix). Microbial spread in the face of host resistance, but they can eventually involve lymphatics and the systemic vasculature. Thus, a localized infection (abscess) can progress to regional lymphadenitis to bacteremia and eventually to colonization of distant sites.

Within the blood, microorganisms may be transported free or intracellularly: some viruses (e.g., poliovirus), fungi, some protozoa (e.g., African trypanosomes), and all helminths are transported cell-free. *Mycobacteria*, and *Leishmania* and *Toxoplasma* organisms, and transport some viruses (e.g., *Colemania* (*Plasmodium* and *Babesia*). Viruses can also propagate by cell-cell fusion or by transport within noncellular vesicles. Disseminated foci of infection can be single and large (e.g., a solitary abscess or tuberculoma) or multiple (e.g., microabscesses or miliary tuberculosis, miliary referring to the resemblance of foci of infection to millet seeds). Spread by low-virulence or nonvirulent microbes occurs commonly (e.g., with vigorous tooth brushing!) but is usually controlled by host defenses. By contrast, sustained bloodstream invasion with pathogens (viremia, bacteremia, fungemia), manifested by fever, hypotension, and other systemic signs of sepsis. Massive bloodstream invasion can rapidly become fatal, even for previously healthy individuals.

*The major manifestations of infectious disease can arise at sites distant from those of initial microorganism entry.* Measles viruses enter through the airways but chickenpox causes cutaneous rashes, and measles pneumonia; poliovirus enters through the intestine but kills motor neurons. *Schistosoma mansoni* eventually localizes in portal and mesenteric blood vessels, damaging the liver and intestine. The rabies virus travels in a retrograde fashion within nerves, while the varicella-zoster virus hibernates in dorsal root ganglia and travels along nerves to cause skin shingles.

*The placental route is also an important mode of transmission (so-called vertical transmission, in contrast to the more common person-to-person mode of infectious disease transmission).* Infectious organisms can enter the fetus through the cervical orifice or the bloodstream; if they traverse the placenta, severe fetal damage can result. They can cause premature delivery or stillbirth. Viral infections can cause fetal maldevelopment depending on the timing: during the first trimester can cause congenital heart disease, mental retardation, cataracts, or deafness; during the second-trimester rubella infections. Infection also can occur during passage through the birth canal (e.g., conjunctivitis) or through breastfeeding (e.g., CMV, HBV in milk). Maternal transmission of HIV results in infection of untreated children during the first year of life. Maternal transmission of HBV can result in chronic infection.

### Microbial Egress From the Body

For transmission of disease to occur, exit of microorganisms from the host is as important as the entry. Exit can occur by skin shedding, coughing, sneezing, urination, or defecation, or via insect vectors (as well as vertical transmission). Pathogens may be actively spread even though the host is asymptomatic (i.e., during an incubation period or in an immunologically unresponsive host).

Subsequent transmission to the next host depends very much on the hardiness of the particular microorganism. Some can survive for extended periods in dust, food, or water; bacterial spores, protozoan cysts, and thick-shelled helminth eggs can survive outside of their original host. Following defecation many expelled pathogens will persist in fecally contaminated environments and subsequent transmission by ingestion (*fecal-oral route*); hepatitis A and E viruses, poliovirus, and some helminths (e.g., hookworms, schistosomes) into stool gain access to new hosts by larval penetration. Less hardy microorganisms must be quickly passed from person to person, often by direct contact (e.g., skin-to-skin) or by blood-borne transmission. Bacteria and fungi can be spread by the respiratory route (e.g., tuberculosis) or gain access to the airways. Viruses infecting the salivary glands (e.g., Epstein-Barr virus [EBV], Cytomegalovirus [CMV]) are principally spread by kissing or talking. Transmission of HBV, hepatitis C virus, and HIV infections through needle-sharing, cuts, or needle sticks and other accidents.

Microorganisms can be transmitted from animals to humans by invertebrate vectors such as insects (e.g., mosquitoes). They can either passively spread infection or occasionally serve as necessary hosts for microbial replication. Zoonotic infections also occur directly from animals to humans (called *zoonotic infections*), either by direct contact (e.g., with the infected animal (e.g., *Trichinella spiralis*).

Prolonged intimate or mucosal contact during sexual activity allows the transmission of a variety of pathogens (herpesviruses, HIV), bacteria (e.g., *T. pallidum*, *N. gonorrhoeae*, *Chlamydia trachomatis*), fungi (Candida species), and arthropods (*Phthirus pubis*, or crab lice). The organisms that cause sexually transmitted infections can often live outside of the host and so depend on direct person-to-person spread. Many of these microorganisms cause asymptomatic symptoms, so that transmission often occurs from individuals who are unaware of their illness. The urethra, vagina, cervix, rectum, or oropharynx (Chapter 18).

## SUMMARY

**Transmission of Microbes** The ability of a microbe to infect an individual depends on specific virulence factors that allow it to breach host barriers and colonize the host. Factors that include:

- Skin: constantly sloughing keratin layer and normal skin flora
- Respiratory tract: macrophages and mucociliary clearance by bronchial epithelium
- GI tract: viscous mucus secretions, pancreatic enzymes and bile, defensins, and normal flora
- Urogenital tract: repeated flushing and commensal flora

Microorganisms may proliferate locally or spread to other sites depending on their tropisms. The route of secondary transmission of any given infection is related to the hardiness of the particular microbe. Transmission can involve direct contact, fecal-oral routes, blood-borne contact, sexual transmission, vertical transmission, or vectors.





## IMMUNE EVASION BY MICROBES

Once microorganisms have scaled host tissue barriers, the chief remaining obstacle between them and a permanent domicile is the immune system. Throughout evolution, microbes have been engaged in a struggle for survival against the arrayed forces of innate and adaptive immunity. Not surprisingly, microorganisms have developed many strategies to resist and evade these defenses, and such mechanisms are important determinants of microbial virulence and pathogenicity. These include:

*Remaining inaccessible to the host immune system.* Microbes that propagate in the lumen of the intestine (e.g., toxin-producing *Clostridium difficile*) or gallbladder (e.g., *Salmonella typhi*) are concealed from many host immune defenses. Viruses that shed from epithelial luminal surfaces (e.g., CMV in urine or milk and poliovirus in stool) or those that infect keratinized epithelium (poxviruses) are inaccessible to antibodies and complement. Some organisms rapidly invade host cells before the humoral response becomes effective (e.g., malaria sporozoites enter hepatocytes; *Trichinella* enters skeletal muscles). Some larger parasites (e.g., tapeworm larvae) form cysts enshrouded in a dense fibrous capsule that renders the microbe largely inaccessible to host immune cells and antibodies. Viral latency within infected cells is the ultimate strategy; during the latent state (e.g., varicella-zoster virus in dorsal root ganglia), many viral genes are not expressed. Finally, some organisms can circumvent immune defenses by covering themselves with host proteins ("the wolf in sheep's clothing approach"). *Varying or shedding antigens.* Neutralizing antibodies block the ability of microbes to infect cells; this is the basis for vaccination. However, neutralizing antibodies cannot effectively protect against microbes with the capacity to express multiple variants of their surface antigens. The low fidelity of viral RNA polymerases (e.g., in HIV and many respiratory viruses) and the ability to re-assort viral genomes (e.g., influenza viruses) leads to viral antigenic variation. Besides viruses, other classes of microbes also show antigenic variability, all using different strategies (Table 9-6). Thus, there are at least 80 different *S. pneumoniae* serotypes, distinguished by unique capsular polysaccharides; the problem is that an antibody produced in response to one serotype does not usually cross-react with another. Another approach is used by *Borrelia* spirochetes (including those that cause Lyme disease), which repeatedly switch their surface antigens. Yet another strategy is used by *S. mansoni*, which shed their antigens within minutes of penetrating the skin, preventing recognition by antibodies. *Resisting innate immune defenses.* Cationic antimicrobial peptides (CAMPs), including *defensins*, *cathelicidins*, and *thrombocidins*, provide important innate defenses against microbes; CAMP resistance is key to the virulence of many bacterial pathogens, allowing them to avoid neutrophil and macrophage killing. The carbohydrate capsules on many bacteria that cause pneumonia or meningitis shield bacterial antigens from circulating antibodies and complement proteins and also prevent neutrophil phagocytosis. Other bacteria make proteins that frustrate phagocytosis, kill phagocytes, prevent their migration, or diminish their oxidative burst. Thus, *S. aureus* expresses protein A molecules that bind the Fc portion of antibodies and so inhibit phagocytosis. *Neisseria*, *Haemophilus*, and *Streptococcus* all secrete proteases that can degrade antibodies. Several viruses, rickettsiae, some intracellular bacteria (including mycobacteria, *Listeria*, and *Legionella*), fungi (e.g., *Cryptococcus neoformans*), and protozoa (e.g., leishmania, trypanosomes, toxoplasmas) have developed strategies to resist intracellular killing and can, therefore, multiply within macrophages even after phagocytosis. Some viruses (e.g., herpesviruses and poxviruses) produce proteins that block complement activation. Other viruses have developed strategies to combat interferons (IFNs), an early host defense against

developed strategies to combat infections (Table 9-6), an early host defense against viruses; inactive homologues of IFN- $\alpha/\beta$  or proteins that inhibit intracellular signaling downstream of IFN receptors can all block the antiviral effects of IFNs. Viruses also can produce inactive homologues of chemokines or chemokine receptors; these act as "decoys" and inhibit recruitment of inflammatory cells. Viruses also can produce soluble cytokine mimics; EBV produces a homologue of the immunosuppressive cytokine IL-10. *Inhibiting adaptive immunity.* Some microbes use a strategy of reducing the ability of CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> cytotoxic T cells to recognize infected cells. For example, several DNA viruses (e.g., CMV and EBV) inhibit production of major histocompatibility complex (MHC) class I proteins or alter their intracellular trafficking, impairing peptide presentation to CD8<sup>+</sup> T cells and preventing killing of infected cells. Although reduced MHC class I expression might be expected to trigger NK cell killing, herpesviruses are one step ahead in that they also express MHC class I homologues that inhibit NK activity (Chapter 5). Similarly, herpesviruses can target MHC class II molecules for early degradation, impairing antigen presentation to CD4<sup>+</sup> T helper cells. Finally, viruses can directly infect lymphocytes and thereby compromise their function; HIV infection (with subsequent cell death) of CD4<sup>+</sup> T cells, macrophages, and dendritic cells is but one example.

**Table 9-6. Pathogens with Significant Antigenic Variation**

Pathogen	Disease
Rhinoviruses	Colds
Influenza virus	Influenza
<i>Neisseria gonorrhoeae</i>	Gonorrhea
<i>Borrelia hermsii</i>	Relapsing fever
<i>Borrelia burgdorferi</i>	Lyme disease
<i>Trypanosoma brucei</i>	African sleeping sickness
HIV	AIDS

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page 331

## SUMMARY

### Immune Evasion by Microbes

After bypassing host tissue barriers, infectious microorganisms must also evade host innate and adaptive immunity to successfully proliferate and be transmitted to the next host. Strategies include:

Remaining inaccessible to host defenses, either in areas not reachable by antibodies or mononuclear cells (e.g., GI tract lumen or epidermis), inside cells, or enshrouded within host proteins  
Constantly changing antigenic repertoires  
Inactivating antibodies or complement, resisting phagocytosis, or growing within phagocytes after ingestion  
Suppressing the host adaptive immune response, e.g. by inhibiting MHC expression and antigen presentation.







## HOW MICROORGANISMS CAUSE DISEASE

Infectious agents can be divided into those that are generally capable of causing disease (*pathogens*) and those that do not have the same probability of causing disease. This is partially a result of host variation in the status, co-morbid disease, immune status). However, it is mostly because different organisms have the ability to cause disease. High virulence connotes the capacity to cause disease in an otherwise healthy host. Low virulence means that the agent causes disease only in particularly susceptible populations (for example, certain bacteria cause disease only in damaged heart valves). *Opportunistic infections* are those in which normally nonpathogenic organisms cause disease in an immunocompromised host. As in real estate ("location is everything"), location in the body is also important. Thus, *E. coli* organisms in the colon are completely normal, whereas *E. coli* infecting the urinary bladder causes cystitis.

Having reviewed the manner by which infectious agents breach host barriers, we next examine how they cause damage. There are three general mechanisms:

Infectious agents can bind to or enter host cells and directly cause cell death or dysfunction. Some release exotoxins that kill cells (or affect their function) at a distance, release enzymes that degrade host tissues, and damage blood vessels and cause ischemic injury. Pathogens can induce host immune and inflammatory responses that cause tissue damage.

### Mechanisms of Viral Injury

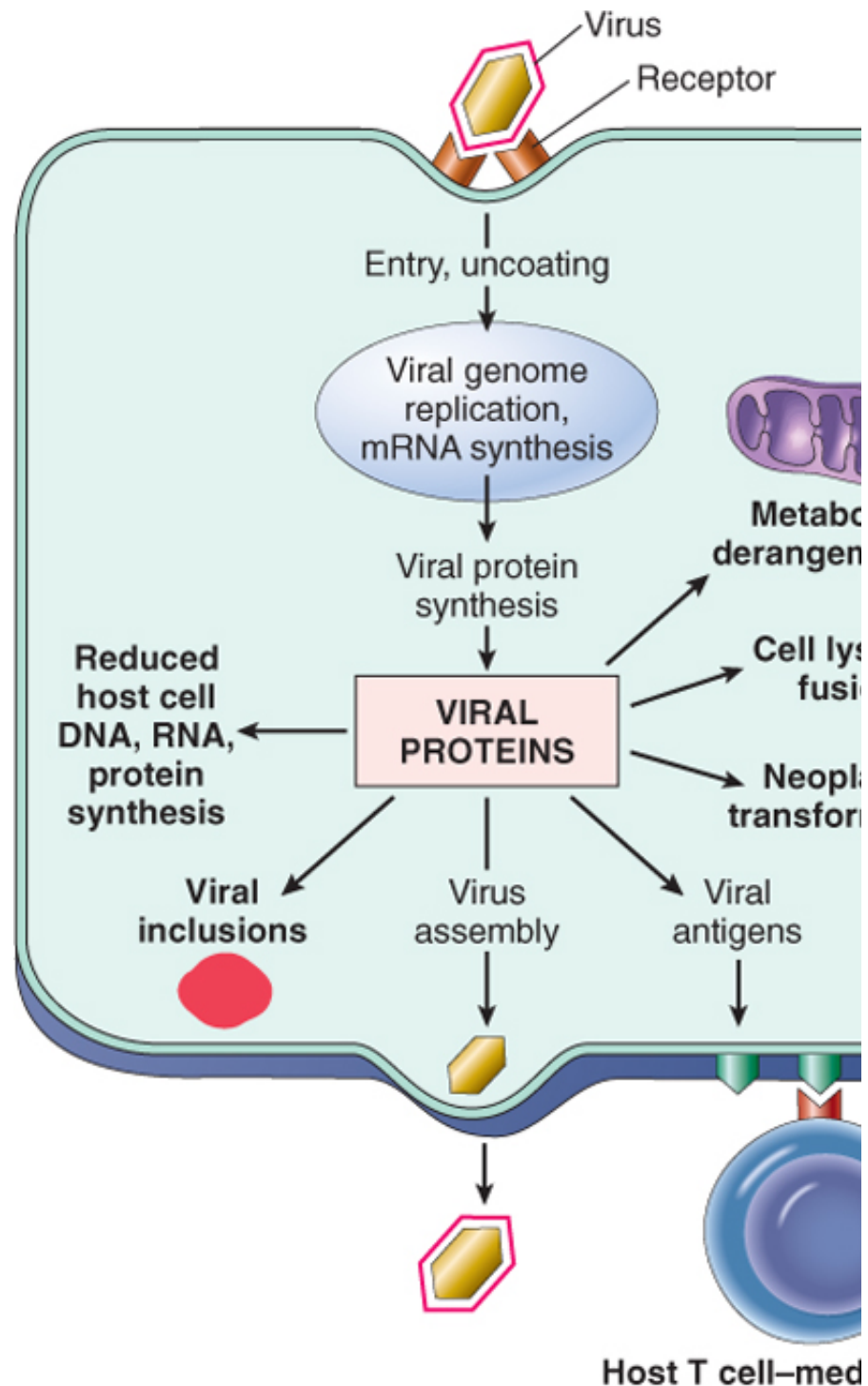
*Viruses can directly damage host cells by entering them and replicating at the host's expense.* The ability of one virus to enter one cell and not others is called tissue tropism and is determined by several factors:

*Host-cell receptors for a particular virus.* Viruses possess specific cell surface proteins that bind to specific receptors on the host cell. Many viruses use normal cellular receptors of the host to enter cells. Thus, HIV binds to the chemokine receptors CXCR4 (T cells) or CCR5 (macrophages). Rhinoviruses bind to the same adhesion molecule used by lymphocytes to facilitate migration and activation at certain sites. In some cases, host proteases are needed to permit viral binding to host cells (e.g., a host protease cleaves viral hemagglutinin). *Cell type-specific transcription factors that recognize viral enhancer and promoter sequences.* For example, the JC virus, which causes progressive multifocal leukoencephalopathy (Chapter 23), is restricted to glial cells because the promoter and enhancer DNA sequences upstream from the viral genome are recognized by transcription factors in glial cells. *Physical barriers.* For example, enteroviruses replicate in the intestine and are inactivated by acids, bile, and digestive enzymes. Rhinoviruses replicate only within the upper respiratory tract and survive optimally at the lower temperature of the upper respiratory tract.

Once viruses are inside host cells, they can injure or kill in several ways (Fig. 9-5):

*Lysis of host cells.* Viral replication interferes with normal cellular functions and may lead to cell death. Release of new virus particles is the mechanism by which influenza virus kills respiratory epithelial cells, yellow fever virus kills liver cells, and rabies destroys neurons. *Immune cell-mediated killing.* Viral proteins expressed by the infected cell can be recognized by the immune system and induce attack by cytotoxic T lymphocytes. Although this can clear infected cells, it can clearly lead to significant host injury. Thus, liver cell injury during HBV infection is due to lymphocyte-mediated destruction of infected hepatocytes. *Alteration of apoptosis pathways.* Some viral proteins (e.g., TAT and gp120 of HIV and adenovirus E1A) induce apoptosis. Indeed, this may be a protective mechanism to clear infected cells. In contrast, some viruses encode genes that inhibit apoptosis (e.g., homologous to Bcl-2). Such strategies may enhance viral replication and promote persistent viral infections, but they may also lead to cancer. *Induction of cell proliferation and transformation, resulting in cancer.* Examples include human papillomavirus and T-cell leukemia/lymphotropic virus-1. The mechanisms of viral transformation are discussed in Chapter 24.

*RNA, or protein synthesis.* These effects may eventually cause cell death, or they may lead to other effects. For example, poliovirus inactivates a cap-binding protein essential for translation of host cell mRNA. Translation of poliovirus mRNA remains unaffected. *Damage to plasma membranes.* Viral proteins can damage plasma membranes and thereby alter their integrity or promote cell fusion (e.g., HIV, measles virus). *Interference with antimicrobial defense, leading to secondary infections.* For example, viral damage to the respiratory tract can lead to subsequent bacterial pneumonia, and HIV depletion of CD4<sup>+</sup> helper T lymphocytes leads to opportunistic infections.



## Mechanisms of Bacterial Injury

The ability of bacteria to cause disease (virulence) depends on their ability to (1) *adhere to host cells*, (2) *penetrate host defenses*, and (3) *deliver toxins that damage cells and tissues*. Pathogenic bacteria have virulence genes that encode these properties. Differences in a small number of virulence genes determine whether an isolate of *Salmonella* causes a threatening infection or will be relatively benign. The coordination of bacterial adherence and toxin production is such that the genes encoding the relevant proteins are frequently co-regulated by specific environmental signals that induce expression of virulence factors as their concentration in the tissues increases, thereby over-

### Bacterial Adherence to Host Cells

*Adhesins* are bacterial surface molecules that bind to host cells; they typically have rather limited cell specificity.

*Fibrillae* cover the surface of gram-positive bacteria; fibrillae on *Streptococcus pyogenes* are composed of *teichoic acids* (see Fig. 9-2). *Lipoteichoic acids* are hydrophobic and bind to fibronectin and buccal epithelial cells, leading to phagocytosis. *Protein F* binds to fibronectin (see Fig. 9-2), and it may also help facilitate *S. pyogenes* phagocytosis.

*Fimbriae* (or *pili*) are filamentous proteins on Gram-negative bacteria (see Fig. 9-2). Although some bacteria, most are involved in adherence. Their stalks are composed of conserved repeating proteins, but the tips are variable and determine binding specificity. For example, *E. coli* strains that cause UTIs bind to a gal(α1-4)gal carbohydrate motif expressed on urothelium. Pili on *N. gonorrhoeae* mediate adherence and can also act as targets for host antibody formation; subsequent variation in pili is an important mechanism by which *N. gonorrhoeae* can escape the immune response.

### Virulence of Intracellular Bacteria

Facultative intracellular bacteria infect epithelial cells (*Shigella* and enteroinvasive *E. coli*), macrophages (*Leishmania*), or both (*S. typhi*). Intracellular growth is a strategy that not only allows escape from certain host defenses (e.g., antibodies) but can also facilitate bacterial spread within the body; thus, macrophage migration carries bacteria to other sites. The virulence factors of intracellular bacteria concern their ability to (1) bind and enter

**Entry into cells.** The host immune response is occasionally subverted to allow bacterial entry. For example, complement C3b-coated (opsonized) bacteria are avidly phagocytized by macrophages. Fibrinogen or complement C2a fragment or activate the alternative complement pathway, with either pathway leading to opsonization; once coated with C3b, *M. tuberculosis* binds to the CR3 complement receptor and is endocytosed. **Intracellular survival.** Once in the cytoplasm, bacteria have different strategies. For epithelial targets, *Shigella* and *E. coli* inhibit host protein synthesis, replicate rapidly, and escape the lysosomes. Macrophages present a different obstacle; once phagocytosed by macrophages, most bacteria are destroyed in lysosomes. Thus, if bacteria are to thrive inside macrophages, they must escape this destruction. *Salmonella* accomplishes this by blocking phagosome-lysosome fusion, permitting unfettered intracellular growth. *Listeria monocytogenes* accomplishes this by escaping the phagosome to proliferate in the cytoplasm; it forms a protein called listeriolysin O and two phospholipases that degrade the phagosome membrane.

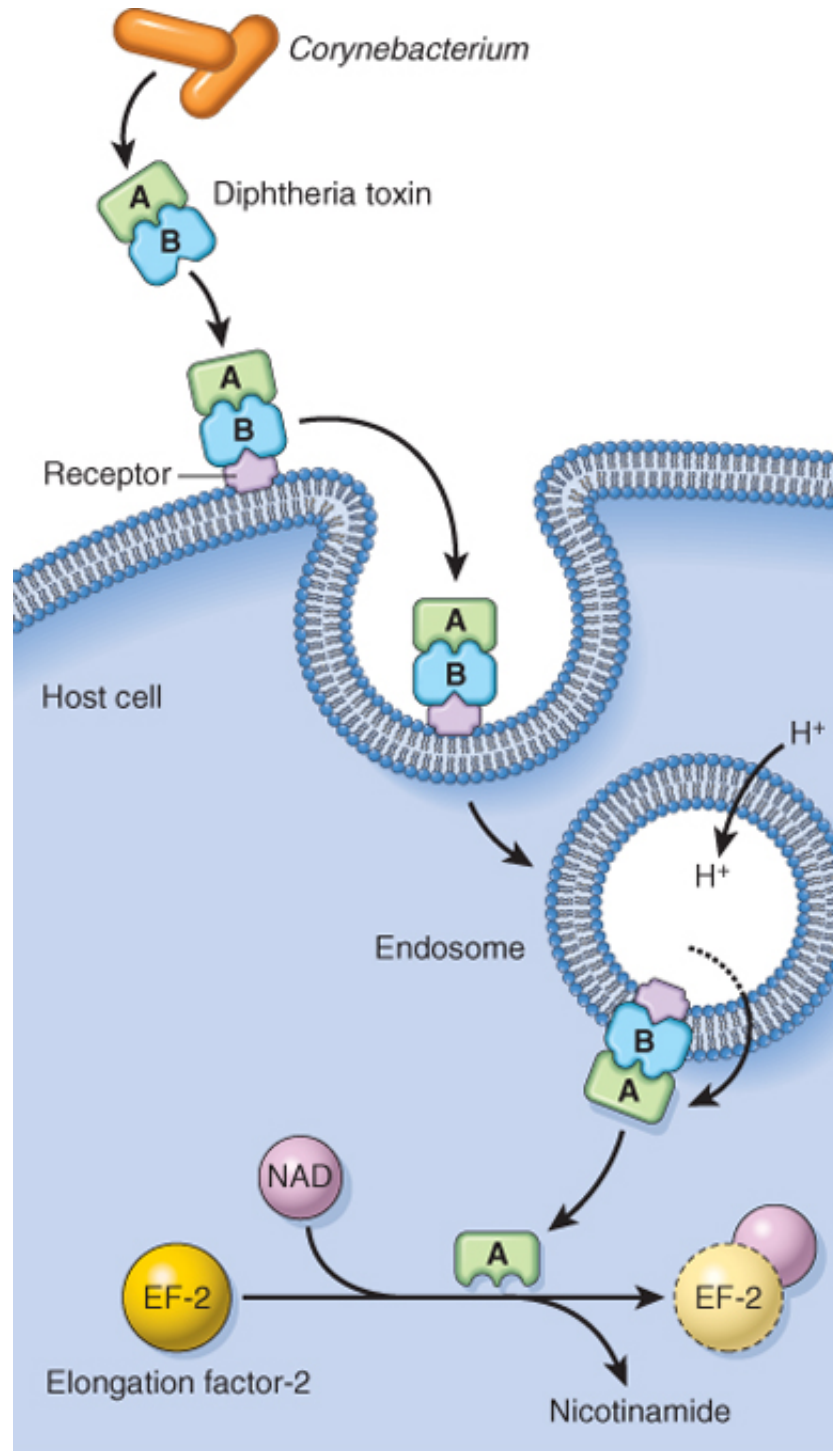
### Bacterial Endotoxin

**Bacterial endotoxin** is a lipopolysaccharide (LPS) that is a major component of the outer cell wall of gram-negative bacteria. LPS is composed of a long-chain fatty acid anchor (lipid A) connected to a core sugar chain, both of which are common to all gram-negative bacteria. Attached to the core sugar is a variable carbohydrate chain (O antigen), which can be used to distinguish between strains. Free LPS attaches to a circulating LPS-binding protein, and the complex then binds to a specific receptor on macrophages, and neutrophils. Engagement of CD14 results in intracellular signaling via an associated protein, leading to cell activation and production of effector cytokines (Chapter 2). TLR-4 engagement on endothelial cells leads to cell activation and a net prothrombotic state (Chapter 4).

The host response to LPS can be both beneficial and harmful. At low levels, LPS induces many ir-

well as increased expression of costimulatory molecules, resulting in leukocyte recruitment and activation. However, at high levels, LPS can precipitate septic shock, disseminated intravascular coagulation syndrome, mainly through overexuberant induction of cytokines such as tumor necrosis factor (TNF).

### Bacterial Exotoxins



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Figure 9-6 Inhibition of cellular protein synthesis by diphtheria toxin. See text for abbreviations. (Adapted from Coll  
Microbiology. New York, Harper & Row, 1990.)

Exotoxins are secreted proteins that directly cause cellular injury and frequently underlie disease.

Some exotoxins are bacterial enzymes (proteases, hyaluronidases, coagulases, fibrinolysins) that contribute to normal bacterial housekeeping and survival. Nevertheless, they can contribute to the manifestations of an infection. Thus, *Staphylococcus aureus* proteases cleave epidermal proteins and presumably lead to easier cutaneous invasion; at the same time they cause desquamation. Gangrene produces an  $\alpha$  toxin (lecithinase) that disrupts plasma membranes, including those of red blood cells. Clostridia literally digest host tissues, including the relatively resistant collagens. Other exotoxins are involved in adhesion or survival but nevertheless cause a distinct disease entity. Thus, the punctate, erythematous lesions of *scarlet fever* is due to a phage-encoded pyrogenic exotoxin made by only certain *Streptococcus pyogenes*. Some exotoxins alter intracellular signaling or regulatory pathways. Most of these have an enzymatically active A subunit and a B subunit that binds receptors on the cell surface and delivers the A subunit into the cell. Within the cytoplasm, the disulfide bond of the toxin is reduced and broken, releasing the active A subunit. In the case of diphtheria toxin the A subunit catalyzes transfer of **adenosine** diphosphate (ADP) to the EF-2 (an elongation factor that is critical for polypeptide synthesis). One toxin molecule can thereby kill a cell by ADP-ribosylating more than  $10^6$  EF-2 molecules. *Clostridium botulinum* elaborates such a toxin to create a layer of dead cells in the throat, on which the bacteria undergo further dissemination. Diphtheria toxin causes serious disease manifestations through neurotoxic effects. Labile enterotoxins of *V. cholerae* and *E. coli* also have an A-B structure and are ADP-ribosylating toxins that catalyze transfer from NAD to the guanyl nucleotide-dependent regulatory component of a cyclic **adenosine** monophosphate (cAMP), causing intestinal epithelial cells to secrete isotonic fluid, resulting in diarrhea and loss of water and electrolytes ([Chapter 15](#)). Neurotoxins, such as those produced by *Clostridium tetani*, inhibit release of neurotransmitters, resulting in paralysis. These toxins have domains that interact specifically with proteins involved in synaptic neurotransmitter release. Botulism is a death from respiratory failure due to paralysis of the chest and diaphragm muscles. Superantigens are capable of stimulating large populations of T lymphocytes, functionally resulting in a "cytokine storm." They bind to class II molecules on antigen-presenting cells, without the usual internal processing, and through their interaction with TCRs. Such MHC II-TCR bridging through the superantigens leads to widespread activation of T cells, massive cytokine release, in particular TNF; the high cytokine levels in turn cause capillary leakage, shock, and multisystem organ failure. *Staphylococcus aureus* and *Streptococcus pyogenes* (i.e., the toxic shock syndrome toxin) are examples of superantigen-producing bacteria.

It has recently been appreciated that many bacteria can live either free in solution or in colonies called *biofilms*. These colonies can form on heart valves or intravascular catheters. Their significance is that they activate many bacterial genes that are not expressed in the free-living forms. Because of the complex colony architecture, microbes in biofilms may be orders of magnitude more resistant to antibiotics.

### Mechanisms of Host-Mediated Immune Injury

As noted earlier, host immune responses to microbes can themselves be the cause of tissue injury. In the case of an inflammatory reaction to *M. tuberculosis*, sequestration of the bacilli and prevention of spread, it also produces the liver damage occurring after HBV infection of hepatocytes is due to the immune response against the virus. Humoral immune responses can also have pathologic sequelae. For example, antibodies that form in the setting of certain streptococcal infections can bind to cross-reactive cardiac myosin (Chapter 11).  $\beta$ -hemolytic streptococcal infections can also induce the formation of streptococcal antigen-antibody complexes that deposit in renal glomeruli and lead to poststreptococcal glomerulonephritis (Chapter 14).

### Patterns of Inflammatory Responses to Infection

Although infectious microorganisms themselves are wildly diverse, the infected host actually has a limited repertoire of responses. Thus, at the microscopic level many pathogens evoke similar reaction patterns, rarely with any fever. Nevertheless, the different patterns of response do suggest particular classes of causative agents. We will make an educated guess about the responsible microbe.

Broadly speaking, there are five histologic patterns of tissue reaction, described next.



Broadly speaking, there are five histologic patterns of tissue reaction, described next.

### *Suppurative Inflammation*

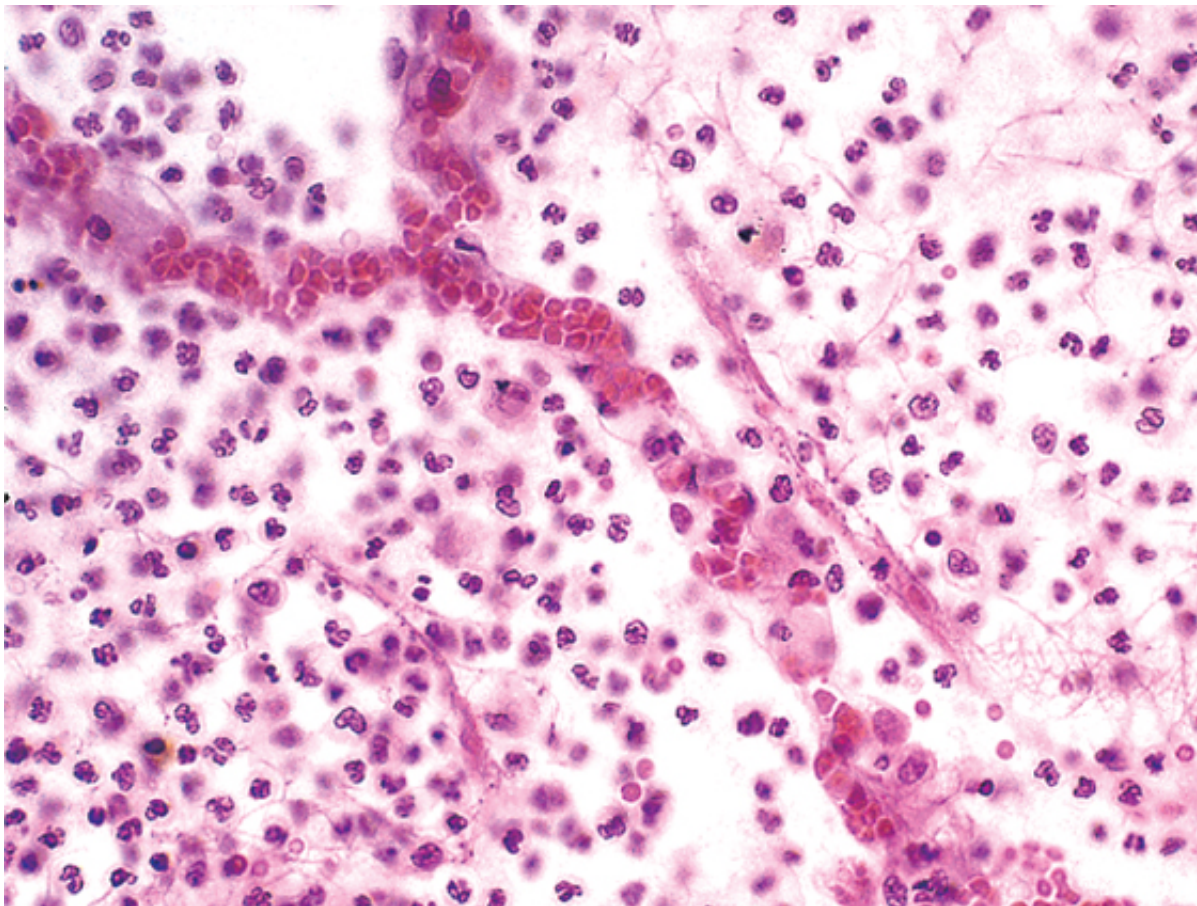
This pattern is the reaction to acute tissue damage ([Chapter 2](#)), characterized by increased vascular permeability and predominantly neutrophils ([Fig. 9-7](#)). In many cases, this is a response to *extracellular bacteria*. The response is attracted to the site of infection by chemoattractants released from "pyogenic" organisms and from host cells.

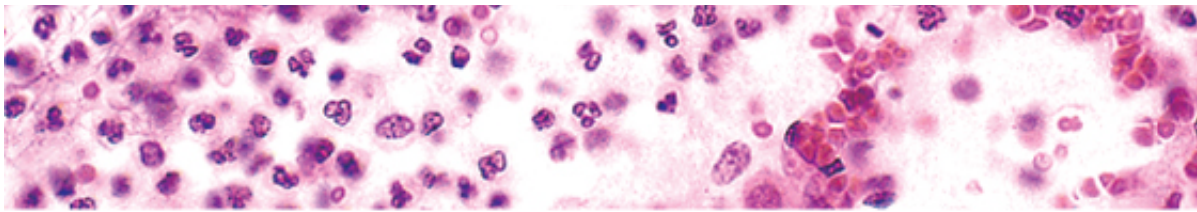
#### **Morphology**

Collections of neutrophils may give rise to localized liquefactive necrosis, forming a **pus**, and bacteria that evoke pus formation. Typically, these are extracellular Gram-positive cocci and Gram-negative rods. They vary from tiny microabscesses formed by bacteria seeding from an infected heart valve to large abscesses of the fallopian tubes caused by *N. gonorrhoeae*, to diffuse involvement of the meninges in meningitis, to entire lobes of the lung during pneumonia. The extent to which the lesion depends on their location and the organism involved. Thus, *S. pneumoniae* usually resolves the lung, and even lobar streptococcal pneumonias typically resolve completely with resolution of the infection ([Fig. 9-7](#)). On the other hand, staphylococcal and *Klebsiella* species destroy alveoli and form abscesses that heal with scar formation. Bacterial pharyngitis resolves without sequelae, but acute bacterial infection of a joint can destroy it in a few days.

### *Mononuclear and Granulomatous Inflammation*

Diffuse mononuclear interstitial infiltrates are a common feature of all chronic inflammatory processes. They are often a response to viruses, intracellular bacteria, or intracellular parasites. In addition, spirochetes elicit inflammatory responses.

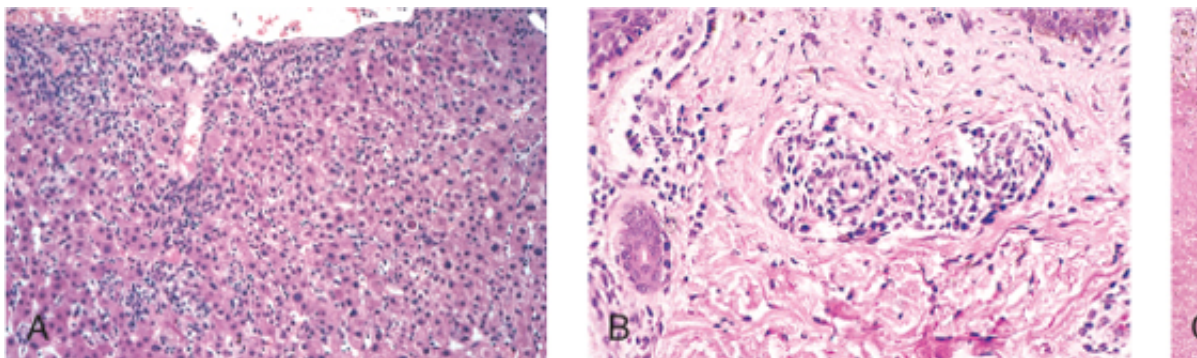




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Figure 9-7 Suppurative (polymorphonuclear) inflammation occurring in a pneumococcal pneumonia. Note the intra alveolar septa.

### Morphology

Which mononuclear cell predominates within the inflammatory lesion depends on the organism. Thus, lymphocytes predominate in HBV infection (Fig. 9-8A), which is common in the primary and secondary lesions of syphilis (Fig. 9-8B). The presence of these cells reflects cell-mediated immune responses against the pathogen or pathogen-infected cells. **Granulomatous inflammation** is a distinctive form of mononuclear inflammation usually evoked by organisms that resist eradication (e.g., *M. tuberculosis*, *Histoplasma capsulatum*, schistosome eggs). It is characterized by the accumulation of activated macrophages called "epithelioid" cells, multinucleated giant cells. In some cases, there is a central area of caseous necrosis (Fig. 9-8C).



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Figure 9-8 Mononuclear and granulomatous inflammation. **A**, Acute viral hepatitis characterized by a predominant infiltrate of lymphocytes and plasma cells in the portal tracts. **B**, Syphilis showing a perivascular infiltrate of lymphocytes and plasma cells. **C**, Granulomatous inflammation with caseation (*asterisk*), which normally forms the center of the granuloma, with a surrounding rim of activated epithelioid cells (*arrows*); this, in turn, is surrounded by a zone of activated T lymphocytes. This is a high-magnification view of a granulomatous response typically forms a three-dimensional sphere with the offending organism at its center.

The final common pathway of many infections is chronic inflammation, which can lead to extensive tissue damage. Infection may cause cirrhosis of the liver, in which dense fibrous septae surround nodules of regenerating hepatocytes. Exuberant scarring response is the major cause of dysfunction (e.g., the fibrosis of the urinary bladder caused by schistosomiasis) or the constrictive fibrous pericarditis caused by tuberculosis.

### Cytopathic-Cytoproliferative Response

These reactions are usually produced by viruses and are characterized by sparse inflammation and/or cell proliferation (cytoproliferative response).

### Morphology

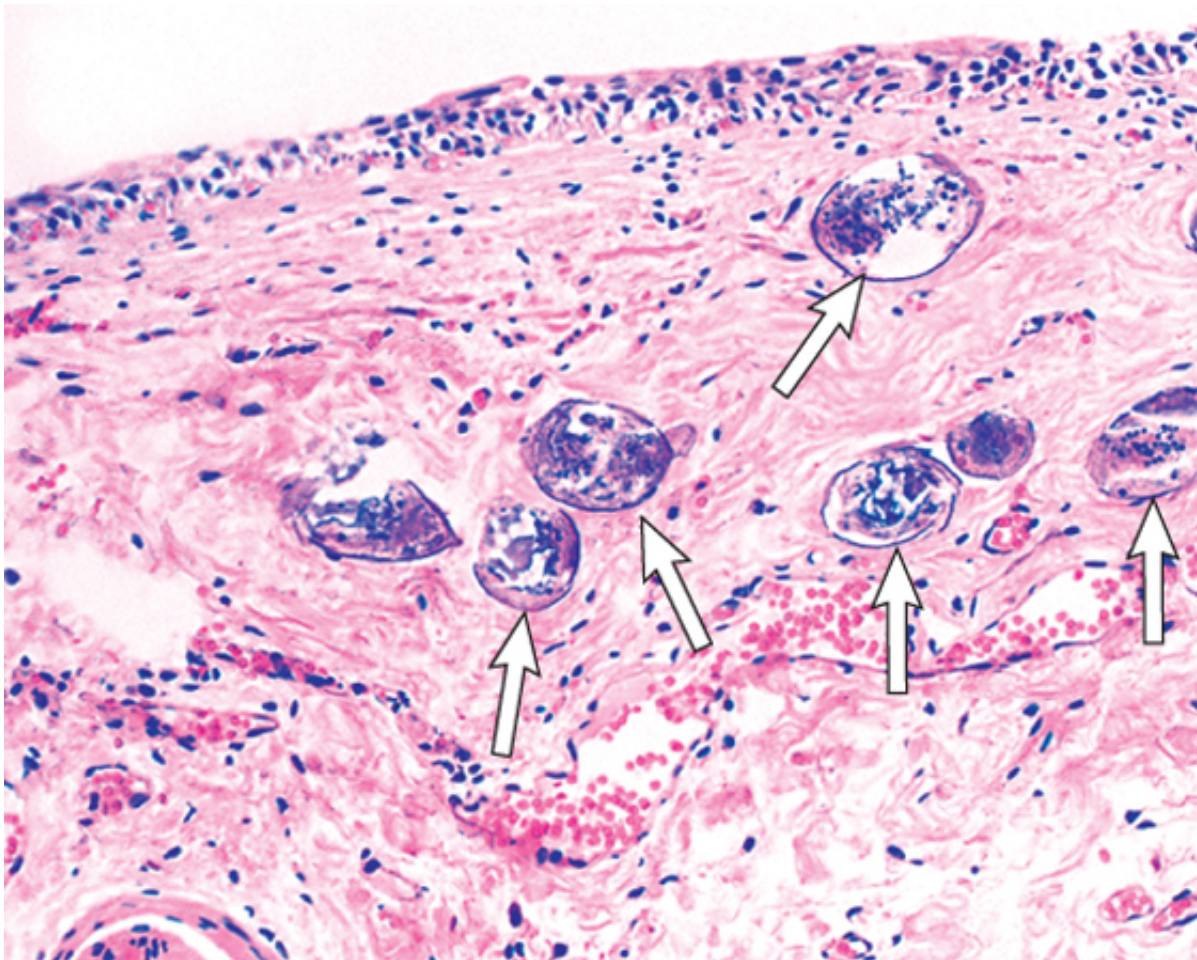
Some viruses replicate within cells and make viral aggregates that are visible as inclusions (e.g., HSV, HBV; see Fig. 9-1) or induce cells to fuse and form polykaryons (e.g., measles virus). Cell damage may cause epithelial cells to become discohesive and form blisters (e.g., herpes simplex virus; see Fig. 9-10). Viruses can also cause epithelial cells to proliferate and take unusual forms (e.g., the koilocytes caused by HPV or the umbilicated papules of molluscum contagiosum caused by poxvirus).



Finally, viruses can cause dysplastic changes and cancers in epithelial cells and lymphocytes.

### *Necrotizing Response*

Some organisms produce potent toxins that cause such rapid and severe necrosis that tissue damage is extensive (e.g., *Clostridium perfringens*). Similarly, *E. histolytica* can cause colonic ulcers and liver abscesses with extensive tissue necrosis without a prominent inflammatory infiltrate.



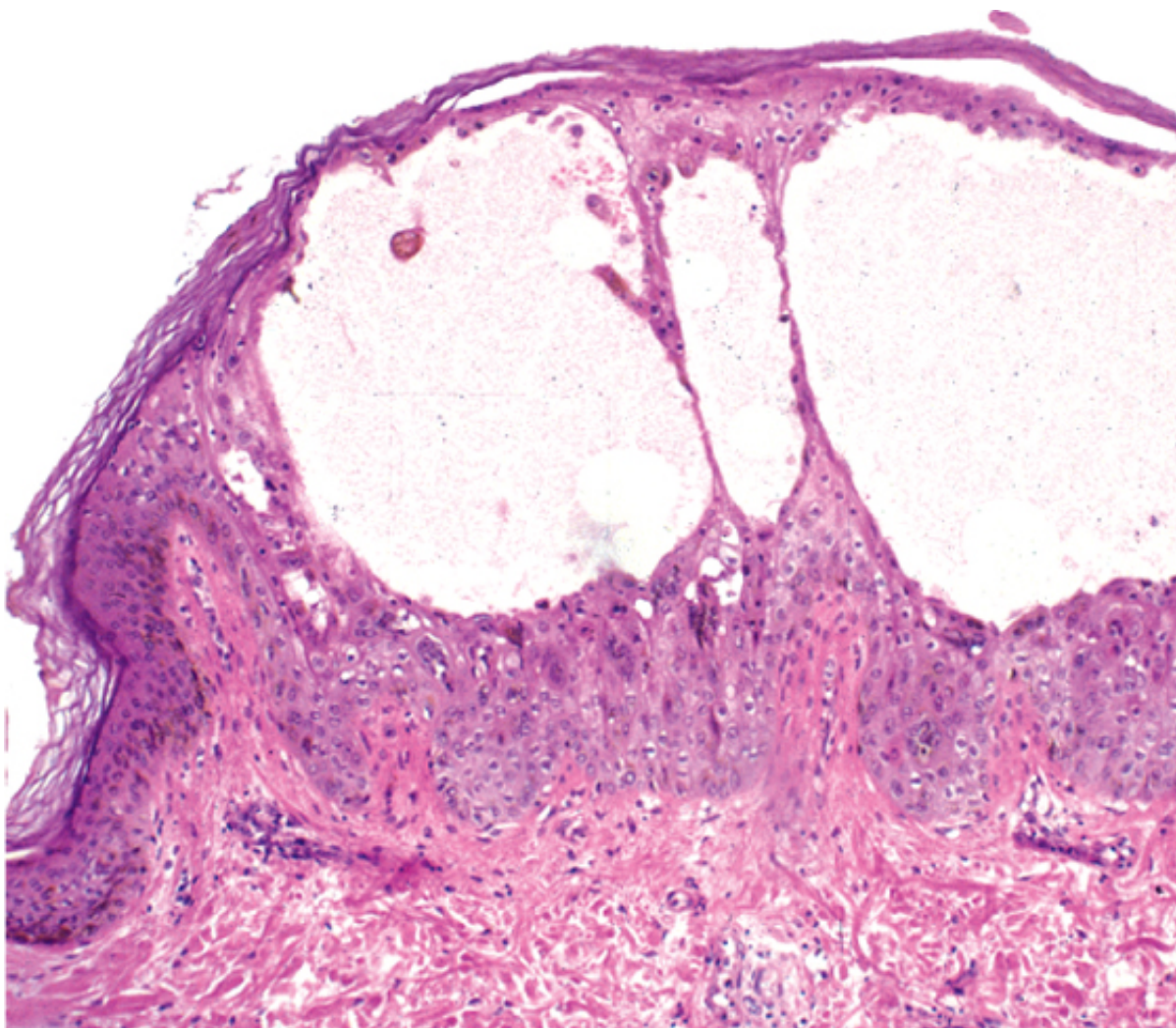
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Figure 9-9 *Schistosoma haematobium* infection of the bladder with numerous calcified eggs (arrows).

### **Morphology**

Because so few inflammatory cells are involved, these lesions resemble infarcts, with pale, anemic areas of necrosis, minimal basophilic nuclear staining and preservation of cellular outlines. Occasionally, by virtue of the inflammatory responses, viruses can cause widespread and severe necrosis of host cells. For example, total destruction of the temporal lobes of the brain by herpesvirus or the liver by hepatitis virus.

### **Infections in the Immunocompromised Host**

Different types of immunodeficiency or immunosuppression affect different cells of the immune system. The types of infections that an immunocompromised individual contracts depend on the types of immune effectors that are deficient. Patients with deficiencies in antibody production and in neutrophils are susceptible to infections with bacteria, fungi, and protozoa. In contrast, deficiencies in T-cell-mediated immunity result in increased susceptibility mainly to viral infections.



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Figure 9-10 Skin lesion of chickenpox (varicella-zoster virus) with intraepithe

Diseases of organ systems other than the immune system can also make patients susceptible to : cystic fibrosis commonly develop respiratory infections with *Burkholderia capacia* (Chapter 13). Bi microbes and allowing infection with pathogens such as *P. aeruginosa*. Loss of splenic function in makes them susceptible to infection with encapsulated bacteria (e.g., *S. pneumoniae*) that are no splenic macrophages. Finally, malnutrition may impair the immune response.

### Morphology

In immunocompromised individuals, the absence of a host inflammatory response of the histologic clues about the potential nature of infecting microorganism(s). For antibody, complement, or neutrophil defects may have severe local bacterial infect significant neutrophilic infiltrate. In these cases, the causal organism may only be i special stains. Although many viral cytopathic effects (e.g., cell fusion or inclusions present, viral infections in immunocompromised hosts may not engender the antici inflammatory response. Indeed, hepatocytes in HBV "carriers" can have a substan burden without inflammation-and without hepatocyte death (Chapter 16). Finally, ir no helper T cells and cannot mount normal cellular responses, organisms that wou granulomatous inflammation (e.g., *M. avium-intracellulare*) present only as sheet with acid-fast bacilli (Fig. 9-11A). A similar phenomenon occurs in some patients w individuals have a strong cell-mediated immune response (so that their lesions cor



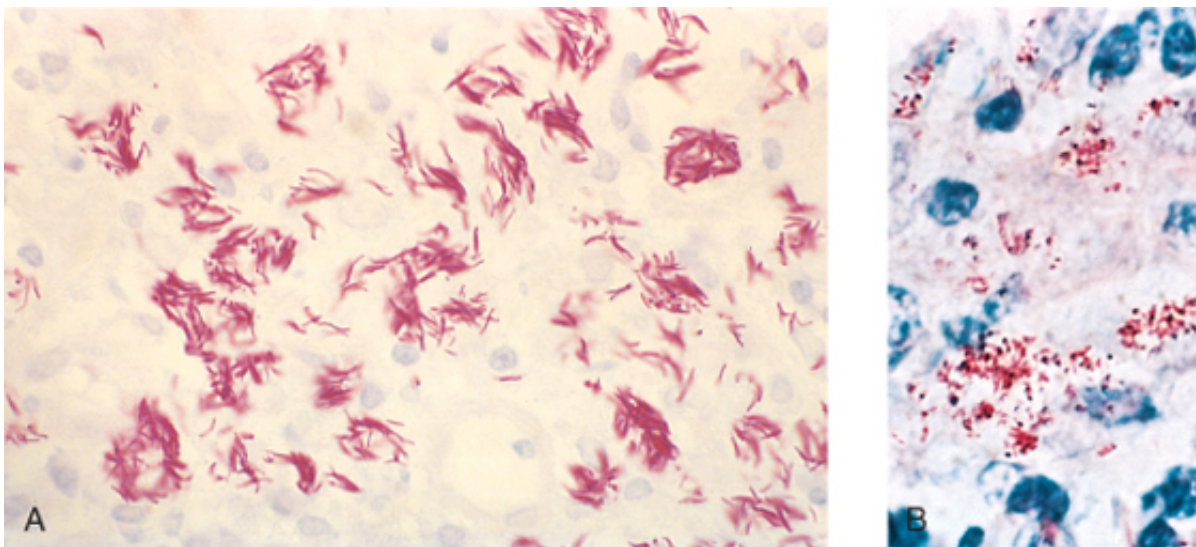
individuals have a strong cell-mediated immune response (so that their lesions are filled with few organisms, i.e., **tuberculoid leprosy**), others have a genetic predilection for a weak immune response to these organisms. As a result, patients in the latter group have lymphocytes with macrophages stuffed with copious organisms (**lepromatous leprosy**).

## SUMMARY

**How Microorganisms Cause Disease** Diseases caused by microbes involve virulence and host responses.

Infectious agents can directly cause cell death or dysfunction by binding to cells. Injury may be due to local or systemic release of bacterial products (LPS), exotoxins, or superantigens. Pathogens can induce immune response damage. Absence of an immune response may reduce the damage in infections; conversely, immunocompromise can allow uncontrolled expansion of agents or of microorganisms that can directly cause injury.

In normal individuals, the patterns of host responses are fairly stereotyped for different microbes; these patterns of responses can be used to infer causal organisms. Suppurative inflammation is typical of many bacteria ("pyogenic" bacteria) and fungi. Mononuclear cell infiltrates are common in many chronic infections and viral infections. Granulomatous inflammation is the hallmark of *Mycobacterium tuberculosis* and some fungi. Cytopathic and proliferative lesions are caused by some viruses.



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Figure 9-11 Host responses in the absence of appropriate T cell-mediated immunity. In both cases, there is no granuloma formation. The organisms persist and even proliferate within macrophages, because either there are inadequate T cells (AIDS) or the T cells are unable to activate macrophages to kill the intracellular pathogens (lepromatous leprosy). **A**, *Mycobacterium avium* infection in a macrophage. **B**, *M. leprae* infection in a macrophage. Both panels show abundant acid-fast bacilli proliferating within macrophages.



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## TECHNIQUES FOR DIAGNOSING INFECTIOUS AGENTS

As discussed above, the histopathology of various infections provides an important clue as to etiology. Moreover, some infectious agents can be directly identified in H+E-stained sections (e.g., CMV or herpesvirus inclusion bodies; bacterial clumps, which usually stain blue; *Candida* and *Mucor* among the fungi; most protozoans; and all helminths). However, many infectious agents are best visualized by special stains that identify organisms on the basis of their cell wall or cell coat characteristics (see [Fig. 9-3](#)), including Gram, acid-fast, silver, mucicarmine, and Giemsa stains; microorganisms can also be identified after labeling with specific antibody probes ([Table 9-7](#)). Regardless of the staining technique, organisms are usually best visualized at the advancing edge of a lesion rather than at its center, particularly if there is necrosis.

Nucleic acid amplification tests such as polymerase chain reaction (PCR) are now used for diagnosis of gonorrhea, chlamydial infection, tuberculosis, and herpes encephalitis; in many cases, molecular assays are much more sensitive than conventional testing. For example, PCR testing of cerebrospinal fluid for HSV encephalitis has a sensitivity of about 80%, while viral culture has a sensitivity of less than 10%. Similarly, PCR-based methods for detecting genital chlamydia identify 10% to 30% more infections than do conventional cultures. Not only are molecular techniques expanding our diagnostic capabilities, genomic sequencing of many pathogens is permitting ever better understanding of the pathogenesis and therapy of infectious diseases.

**Table 9-7. Special Techniques for Diagnosing Infectious Agents**

Gram stain	Most bacteria
Acid-fast stain	Mycobacteria, nocardiae (modified)
Silver stains	Fungi, legionellae, pneumocystis
Periodic acid-Schiff	Fungi, amebae
Mucicarmine	Cryptococci
Giemsa	Campylobacteria, leishmaniae, malaria parasites
Antibody probes	Viruses, rickettsiae
Culture	All classes
DNA probes	Viruses, bacteria, protozoa

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Nucleic acid-based tests are also useful for quantifying several pathogens. For example, the management of hepatitis B and C infections is guided by nucleic acid-based viral quantification or typing to predict resistance to antiviral drugs. In patients with HIV, viral RNA load is used routinely to guide antiretroviral therapy.

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## 10 The Blood Vessels\*

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Vascular disease is responsible for more morbidity and mortality than any other category of human disease. Although the most clinically significant lesions involve arteries, venous pathology can also cause clinical disorders. Vascular pathology results in disease via two principal mechanisms:

*Narrowing or complete obstruction* of vessel lumina, either progressively (e.g., by atherosclerosis) or precipitously (e.g., by thrombosis or embolism) *Weakening* of vessel walls, causing dilation and/or rupture.

We will first describe some of the important anatomic and functional characteristics of blood vessels so we can better understand the diseases that affect them.



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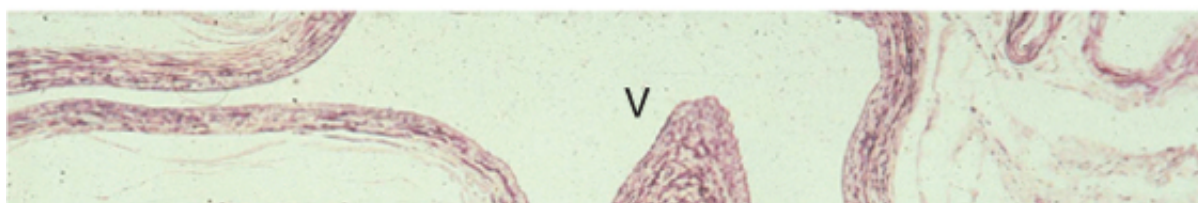
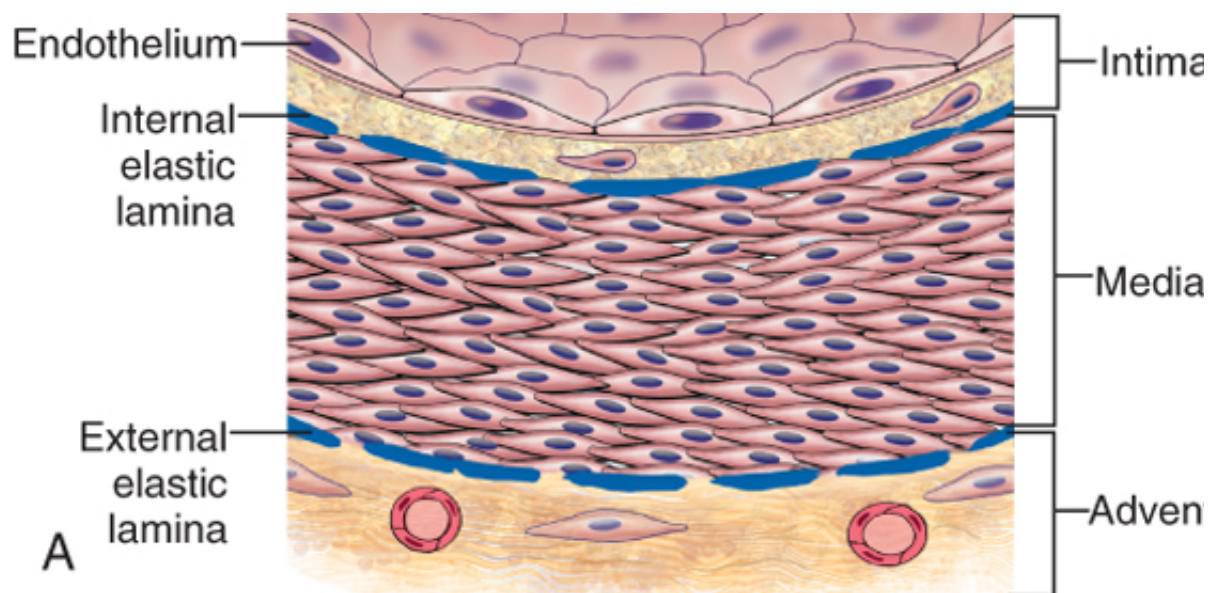
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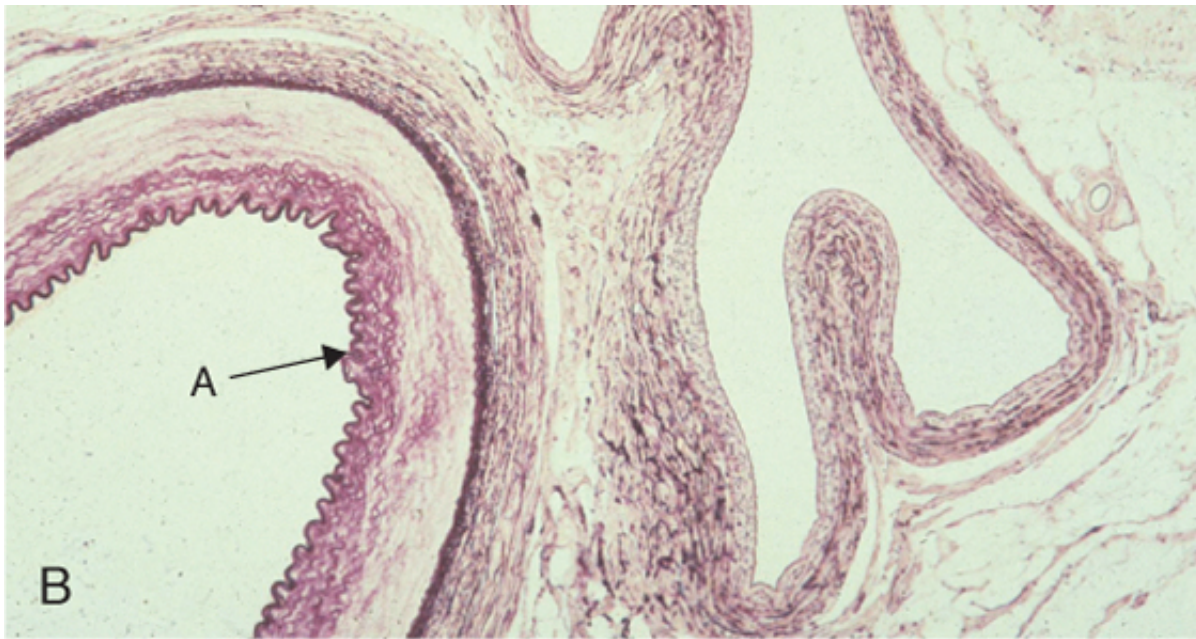
## NORMAL VESSELS

The general architecture and cellular composition of blood vessels are the same throughout the cardiovascular system. However, distinct functional requirements in different locations within the vasculature (see below) result in multiple forms of vascular specialization. As an example, arterial walls are thicker than corresponding veins at the same level of branching to accommodate pulsatile flow and higher blood pressures. Such vessel specialization also means that pathologic lesions within the vascular tree characteristically affect only certain parts of the circulation. Thus, atherosclerosis affects mainly elastic and muscular arteries, hypertension affects small muscular arteries and arterioles, and specific types of vasculitis characteristically involve only vessels of a certain caliber.

Endothelial cells (ECs) and smooth muscle cells (SMCs) constitute the bulk of vessel wall cellular components; the remainder of the wall is composed of extracellular matrix (ECM) including elastin, collagen, and glycosaminoglycans. Vessel walls are organized into three concentric layers: *intima*, *media*, and *adventitia* (Fig. 10-1); these are present to some extent in all vessels but are most apparent in large arteries and veins. In normal arteries, the intima consists of an EC monolayer overlying a thin ECM sheet; the intima is demarcated from the media by a dense elastic membrane called the *internal elastic lamina*. The media is composed predominantly of SMCs and ECM, surrounded by the relatively loose connective tissue, nerve fibers, and smaller vessels of the adventitia; an *external elastic lamina* is present in some arteries and defines the transition between media and adventitia. By virtue of *fenestrations* (holes) in the internal elastic membrane, the innermost medial SMCs receive oxygen and nutrients by direct diffusion from the vessel lumen. However, diffusion from the lumen is inadequate to sustain the SMCs in the outer media in large and medium-sized vessels; in that case, small arteries within the adventitia (termed *vasa vasorum*, literally "vessels of the vessels") supply the outer 50% to 65% of the media.







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Figure 10-1 The vascular wall. **A**, Cross-section from a muscular artery (e.g., coronary artery). **B**, Histology showing artery (A) and adjacent vein (V), with the elastic lamellae stained black (the *arrow* points to the arterial internal elastic lamina). Because it must sustain higher pressures, the artery has a thicker wall with more-organized elastin architecture than in the corresponding vein. Conversely, the vein has a larger lumen with diffusely distributed elastin, permitting greater capacitance. (**B**, Courtesy of Dr. Mark Flomenbaum, Office of the Chief Medical Examiner, Boston, Massachusetts.)

Based on size and structural features, *arteries* are divided into three basic types:

Large, or *elastic arteries*, including the aorta and its large branches (particularly the innominate, subclavian, common carotid, and iliac), and pulmonary arteries. In these arteries, elastic fibers alternate in layers with SMCs. Because of the high content of elastic fibers, the media expands during systole (storing some of the energy of each heartbeat), and elastic recoil of the vessel wall during diastole propels blood through the more distal vessels. Medium-sized, or *muscular arteries*, including smaller branches off the aorta (e.g., coronary and renal arteries). Here, the media is composed primarily of SMCs, with elastin limited to the internal and external elastic lamina. Although arterial wall thickness diminishes with decreasing vessel size, the ratio of thickness to lumen diameter actually increases for these vessels. Small arteries ( $\leq 2$  mm in diameter) and *arterioles* (20–100  $\mu\text{m}$  in diameter), which lie within the interstitial connective tissue of organs. The media here is essentially all SMCs. *Arterioles are the principal control points for regulation of physiologic resistance to blood flow; in arterioles, the pressure and velocity of blood flow are both sharply reduced, and flow becomes steady rather than pulsatile.* The modulation of regional blood flow and blood pressure are accomplished by changes in lumen size through SMC contraction (*vasoconstriction*) or relaxation (*vasodilation*). Because the resistance to fluid flow in a tube is inversely proportional to the fourth power of the diameter (i.e., halving the diameter increases resistance 16-fold), small changes in arteriolar lumen size have profound flow-limiting effects.

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pi

*Capillaries* represent the next level of vascular branching after arterioles. These are approximately the same diameter as a red blood cell (7–8  $\mu\text{m}$ ) and have an endothelial cell lining but no media. Collectively, capillaries have a very large total cross-sectional area, and with thin walls (only one cell thick) and slow flow, they are ideally suited for the rapid exchange of diffusible substances between blood and tissue. Normal tissue function depends on adequate supplies of oxygen and nutrients, and since



diffusion of these components is not efficient beyond 100  $\mu\text{m}$ , the capillary network of most tissue very rich; metabolically active tissues (e.g., heart) have the highest capillary density.

Blood flows from capillary beds into postcapillary venules and then sequentially through collecting venules to progressively larger veins. In the setting of inflammation, vascular leakage and leukocyte emigration occur preferentially in postcapillary venules ([Chapter 2](#)). Relative to corresponding arteries, veins have larger diameters, larger lumina, and thinner, less well-organized walls ([Fig. 10-1B](#)). The veins are more prone to dilation, compression, and easy penetration by tumors and inflammatory processes. Venous pressure and flow velocities are very low; thus, where venous blood has to flow against gravity (e.g., leg veins), reversed flow is prevented by valves. Collectively, the venous system has a huge capacitance, containing approximately two-thirds of all systemic blood.

*Lymphatics* are thin-walled, endothelium-lined channels that drain excess interstitial tissue fluid ([Chapter 2](#)), eventually returning it to blood via the thoracic duct. Lymphatic flow also contains mononuclear inflammatory cells and a host of proteins; by passing through lymph nodes, lymphatics constitute an important pathway for continuous sampling of peripheral tissues for infection. *These channels can also disseminate disease by transporting microbes or tumor cells from distant sites to lymph nodes and eventually to the systemic circulation.*



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## CONGENITAL ANOMALIES

Although rarely symptomatic, variants of the usual anatomic pattern of vascular supply can become important during surgery when a vessel in an unexpected location is injured. Among the congenital vascular anomalies, three are particularly significant, though not necessarily common:

*Developmental, or berry, aneurysms* occur in cerebral vessels. These are small, spherical dilatations typically in the circle of Willis; when ruptured, they can cause fatal intracerebral hemorrhage. They are discussed in greater detail in [Chapter 23](#). *Arteriovenous fistulas* are abnormal, typically small, direct connections between arteries and veins that bypass the intervening capillaries. They occur most commonly as developmental defects but can also result from rupture of an arterial aneurysm into the adjacent vein, from penetrating injuries that pierce arteries and veins, or from inflammatory necrosis of adjacent vessels; intentionally created arteriovenous fistulas are used to provide vascular access for chronic hemodialysis. When arteriovenous fistulas are large or extensive, they can become clinically significant by shunting blood from the arterial to the venous circulations. This forces the heart to pump additional volume, and high-output cardiac failure can ensue. *Fibromuscular dysplasia* is a focal irregular thickening of the walls of medium and large muscular arteries, including renal, carotid, splanchnic, and vertebral vessels. The cause is unknown but is probably developmental. Segments of the vessel wall are focally thickened by some combination of irregular medial and intimal hyperplasia and fibrosis; this results in luminal stenosis and, in the renal arteries, may be a cause of renovascular hypertension ([Chapter 14](#)).





## VASCULAR WALL CELLS AND THEIR RESPONSE TO INJURY

As the main cellular components of the blood vessel walls, ECs and SMCs play central roles in vascular homeostasis. The integrated function of these cells is critical for vasculature to adapt to hemodynamic and biochemical changes.

### Endothelial Cells

ECs form a single-cell-thick continuous sheet (the *endothelium*) that lines the entire vascular system. ECs play a central role in vascular wall homeostasis and circulatory function. ECs contain *Weibel-Palade bodies*, intracellular membrane vesicles containing von Willebrand factor. Antibodies to von Willebrand factor and/or platelet-endothelial cell adhesion molecules (localized to interendothelial junctions) can be used to identify ECs immunohistochemically.

Vascular endothelium is a multifunctional tissue with a wealth of synthetic and metabolic properties. Constitutive activities critical for normal vessel homeostasis ([Table 10-1](#)). Thus, ECs maintain a non-thrombotic surface (until clotting is necessitated by local injury, [Chapter 4](#)), modulate vascular resistance, metabolize and release vasoactive substances, affect the growth of other cell types, particularly SMCs. As a selectively permeable monolayer, endothelium regulates the passage of small and large molecules into the vascular wall and beyond. In most regions, the interendothelial junctions are tight. However, tight EC junctions can loosen under the influence of hemodynamic factors (e.g., high blood flow) or chemical factors (e.g., histamine in inflammation), resulting in the flooding of adjacent tissues by electrolytes and proteins. Leukocytes can slip between adjacent ECs ([Chapter 2](#)).

Although ECs share many general attributes, there is also substantial phenotypic variability depending on the site of origin and adaptation to local environmental cues. For example, endothelia lining hepatocyte cords or in renal glomeruli have fenestrations (holes), while endothelium (and associated perivascular cells) in the central nervous system form a blood-brain barrier.

**Table 10-1. Endothelial Cell Properties and Functions**

<b>Maintenance of Permeability Barrier</b>
<b>Elaboration of Anticoagulant, Antithrombotic, Fibrinolytic Regulators</b>
Prostacyclin
Thrombomodulin
Heparin-like molecules
Plasminogen activator
<b>Elaboration of Prothrombotic Molecules</b>
Von Willebrand factor
Tissue factor
Plasminogen activator inhibitor
<b>Extracellular Matrix Production (Collagen, Proteoglycans)</b>
<b>Modulation of Blood Flow and Vascular Reactivity</b>
Vasconstrictors: endothelin, ACE
Vasodilators: NO, prostacyclin
<b>Regulation of Inflammation and Immunity</b>
IL-1, IL-6, chemokines
Adhesion molecules: VCAM-1, ICAM, E-selectin P-selectin
Histocompatibility antigens
<b>Regulation of Cell Growth</b>
Growth stimulators: PDGF, CSF, FGF
Growth inhibitors: heparin, TGF- $\beta$

## Oxidation of LDL

ACE, angiotensin-converting enzyme; CSF, colony-stimulating factor; FGF, fibroblast growth factor; ICAM, intercellular adhesion molecule-1; LDL, low-density lipoprotein; NO, nitric oxide; PDGF, platelet-derived growth factor; TGF- $\beta$ , transforming growth factor- $\beta$ ; VCAM, vascular cell adhesion molecule-1.

Endothelial injury contributes to a host of pathologies including thrombosis, atherosclerosis, and hypertension. For example, EC denudation stimulates clotting ([Chapter 4](#)) and eventually SMC proliferation (see later). ECs also respond to various stimuli by modulating their constitutive activities and expressing new (inducible) and prothrombotic molecules, growth factors, and other products). *Endothelial dysfunction* is the term used to describe changes in the repertoire of ECs. It can be induced by hemodynamic stresses and lipid metabolites (e.g., oxLDL in atherosclerosis, see below) as well as by cytokines and bacterial products (contributing to the pathogenesis of sepsis). Some changes are rapid (within minutes), reversible, and independent of new protein synthesis (e.g., decreased NO causing venular gaps; [Chapter 2](#)). Other changes require new gene expression and protein synthesis and manifest themselves. The consequences of endothelial dysfunction include impaired endothelium-dependent vasodilation ([Chapter 4](#)), and leukocyte adhesion.

## Vascular Smooth Muscle Cells

SMCs participate in both normal vascular repair and pathologic processes such as atherosclerosis. They have the capacity to proliferate when appropriately stimulated; they can also synthesize ECM collagen, elastin, and growth factors and cytokines. As the predominant cellular element of the vascular media, SMCs are responsible for vasoconstriction or dilation that occurs in response to physiologic or pharmacologic stimuli.

## Intimal Thickening: A Stereotyped Response to Vascular Injury

*Vascular injury-with EC loss or even merely dysfunction-stimulates SMC growth and associated neointima formation.* This process is very much analogous to the physiologic healing process that occurs in any damaged tissue ([Chapter 3](#)). Following endothelial injury SMCs or SMC precursor cells migrate into the intima, proliferate, and produce ECM in the same way that fibroblasts fill in a wound forming a neointima ([Fig. 10-2](#)). This neointimal response is a direct result of damage or dysfunction, including infection, inflammation, immune injury, physical trauma (e.g., balloon angioplasty), or chemical exposure (e.g. oxidized lipids or cigarette smoke). Thus, intimal thickening is essentially the stereotyped response to injury.

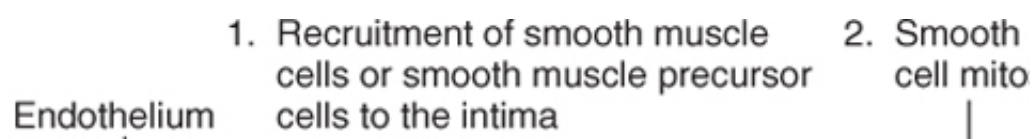
It should be emphasized that the phenotype of neointimal SMCs is distinct from medial SMCs; neointimal SMCs are proliferating, but they do have the capacity to divide. Concurrently, there are decreased contractile protein synthesis, such as rough endoplasmic reticulum and Golgi apparatus, increase.

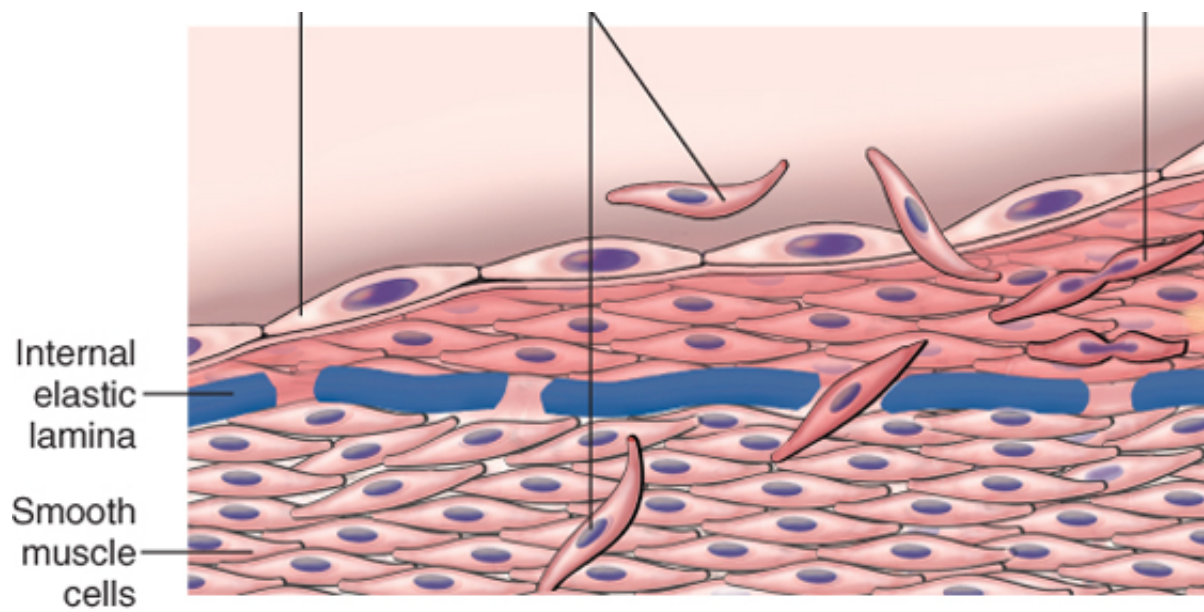
With time and restoration and/or normalization of the endothelial layer, the intimal SMCs can return to their normal state. At that point, the stereotyped healing response has already resulted in intimal thickening that may be irreversible. If the thickening persists, excessive thickening can cause stenosis of small and medium-sized blood vessels (e.g., atherosclerosis), leading to downstream tissue perfusion.

## SUMMARY

### Response of Vascular Wall Cells to Injury

Injury (of almost any type) to the vessel wall results in a stereotypic healing response. The response involves expansion by proliferating SMCs and newly synthesized ECM. The recruitment of SMCs in this process involves signals from cells (e.g., ECs, platelets, and macrophages) and mediators derived from coagulation and complement cascades. Excessive thickening of the vessel wall results in luminal stenosis that blocks vascular flow.





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Figure 10-2 Stereotypic response to vascular injury: Intimal thickening, with smooth muscle cell (SMC) migration and ECM synthesis. Intimal SMCs may derive from the underlying media or may be recruited from circulating precursors. (Modified from Robbins and Cotran: Basic Pathology, 8th ed, Philadelphia, 2004, Elsevier.)



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## ARTERIOSCLEROSIS

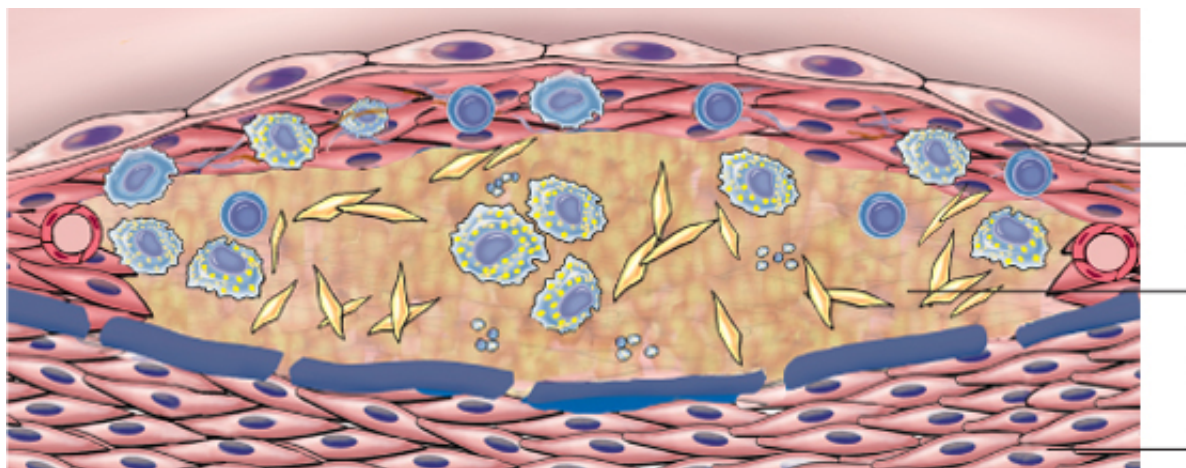
*Arteriosclerosis* literally means "hardening of the arteries"; it is a generic term reflecting arterial wall thickening and loss of elasticity. Three patterns are recognized, with different clinical and pathologic consequences:

*Arteriolosclerosis* affects small arteries and arterioles. The two anatomic variants, hyaline and hyperplastic, are both associated with vessel wall thickening and luminal narrowing that may cause downstream ischemic injury. Arteriolosclerosis is most often associated with hypertension and/or diabetes mellitus and will be discussed in detail later in the section on hypertension. *Mönckeberg medial calcific sclerosis* is characterized by calcific deposits in muscular arteries, typically in persons older than age 50. The radiographically visible, often palpable calcifications, do not encroach on the vessel lumen and are usually not clinically significant. *Atherosclerosis*, from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern (see below).





## ATHEROSCLEROSIS



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Figure 10-3 The major components of a well-developed intimal atheromatous plaque over

Atherosclerosis is characterized by intimal lesions called *atheromas* (also called *atheromatous* or into vascular lumina. An atheromatous plaque consists of a raised lesion with a soft, yellow, grum (cholesterol esters) covered by a firm, white fibrous cap (Fig. 10-3). Besides obstructing blood flow underlying media and can themselves rupture, causing acute catastrophic vessel thrombosis. Ath morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder. B important manifestation of the disease, epidemiologic data related to atherosclerosis mortality typi heart disease (IHD) (Chapter 11); indeed, myocardial infarction is responsible for almost a quarter be minimized, carotid atherosclerotic disease and stroke are also associated with significant morb

### Epidemiology

Virtually ubiquitous among most developed nations, atherosclerosis is much less prevalent in Cer The mortality rate for IHD in the United States is among the highest in the world and is approxima Nevertheless, IHD has been increasing in Japan and is now the second leading cause of death th to the United States and adopt American lifestyles and dietary customs acquire the same predispo homegrown population.

The prevalence and severity of atherosclerosis and IHD among individuals and groups are relatec constitutional (and therefore less controllable) but others acquired or related to behaviors and pot (10-2). Risk factors have been identified through a number of prospective studies in well-defined p (Massachusetts) Heart Study and Atherosclerosis Risk in Communities (Fig. 10-4). *Multiple risk fa* factors increase the risk approximately fourfold. When three risk factors are present (e.g., hyperlip rate of myocardial infarction is increased seven times.

### Major Constitutional Risk Factors for IHD

Age

Table 10-2. Risk Factors for Atherosclerosis

Major Risks	Lesser, Uncertain, or Nonquantitated Risks
<b>Nonmodifiable</b>	Obesity

Increasing age	Physical inactivity
Male gender	Stress ("type A personality")
Family history	Postmenopausal estrogen deficiency
Genetic abnormalities	High carbohydrate intake
	Lipoprotein(a)
<b>Potentially Controllable</b>	Hardened (trans)unsaturated fat intake
Hyperlipidemia	
Hypertension	<i>Chlamydia pneumoniae</i> infection
Cigarette smoking	
Diabetes	
C-reactive protein	

Age is a dominant influence. Although the accumulation of atherosclerotic plaque is typically a process that does not become clinically manifest until lesions reach a critical threshold and begin to precipitate organ injury, in men ages 40 and 60, the incidence of myocardial infarction in men increases fivefold, even though the process is already evolving before that. Death rates from IHD rise with each decade even into advanced age.

#### Gender

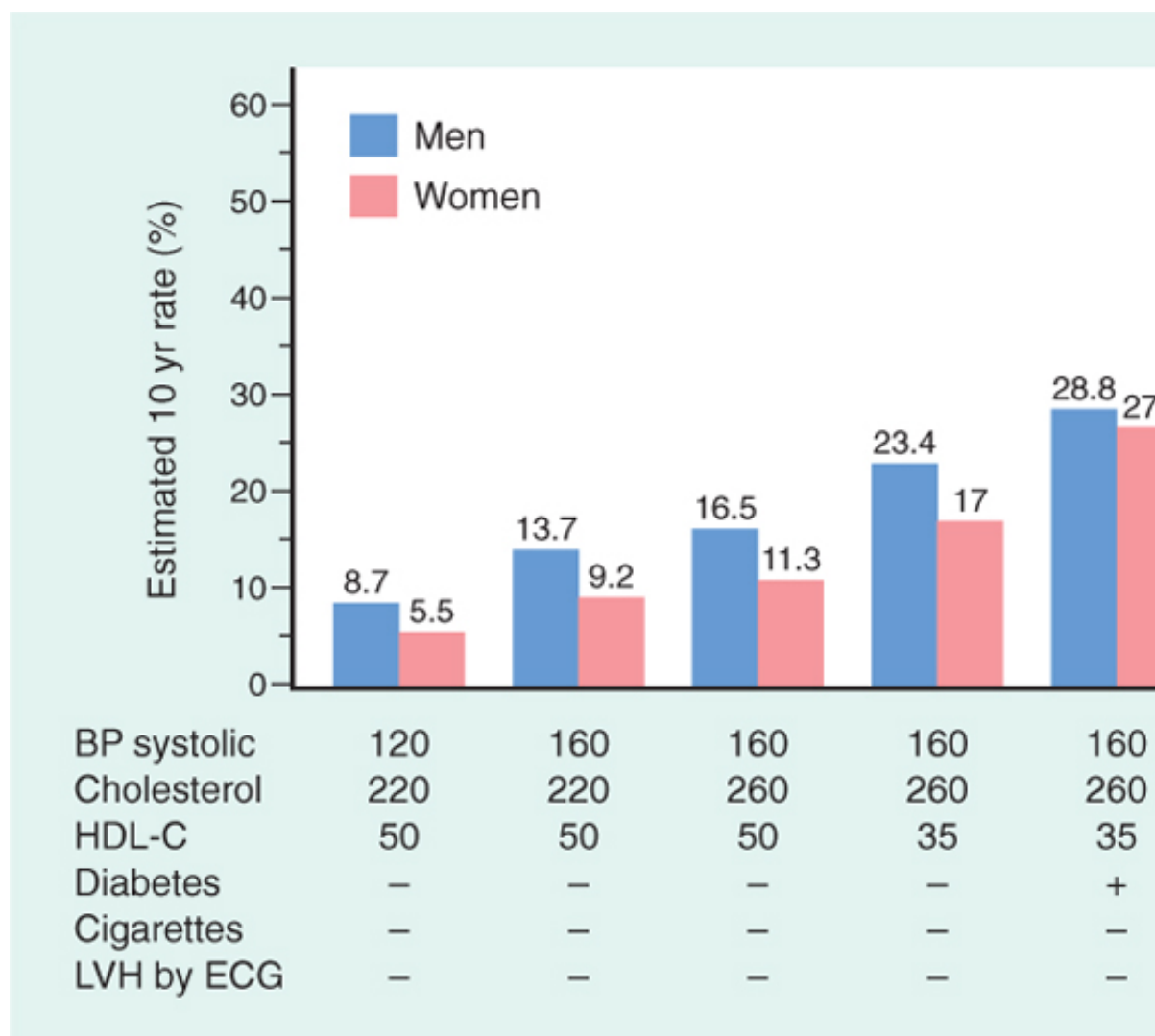


Figure 10-4 Estimated 10-year risk of coronary artery disease in hypothetical 55-year-old men and women as a function of age, blood pressure, smoking, and diabetes. BP, blood pressure; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. (Adapted from O'Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: lessons from observational studies. *Circulation* 1996;94:327-336. permission from Lippincott Williams & Wilkins.)

Other factors being equal, premenopausal women are relatively protected against atherosclerosis compared with age-matched men. Thus, myocardial infarction and other complications of atherosclerosis are uncommon in women who are otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension. After menopause, the risk of atherosclerosis-related diseases increases and with greater age eventually exceeds that of men. The protective effect of estrogen has long been proposed to explain this effect, several clinical trials have failed to demonstrate a benefit of estrogen for cardiovascular disease prevention in either sex; indeed, postmenopausal estrogen replacement probably increases cardiovascular risk and is no longer recommended for preventing heart disease in women. Aside from age, there are a number of parameters that can affect outcomes of IHD; thus, women show differences in hemostatic factors and arterial remodeling.

### Genetics

The well-established familial predisposition to atherosclerosis and IHD is multifactorial. In some cases, the inheritance of other risk factors, such as hypertension or diabetes, whereas in others it involves well-defined genetic defects of lipid metabolism, such as familial hypercholesterolemia (Chapter 7), that result in excessively high blood cholesterol levels.

### Major Modifiable Risk Factors for IHD

#### Hyperlipidemia

*Hyperlipidemia*—more specifically, *hypercholesterolemia*—is a major risk factor for atherosclerosis; a blood cholesterol level of 240 mg/dL is sufficient to stimulate lesion development. The major component of serum cholesterol is low-density lipoprotein (LDL) cholesterol ("bad cholesterol"); LDL cholesterol has an essential role in delivering cholesterol to peripheral tissues. In contrast, high-density lipoprotein (HDL, "good cholesterol") mobilizes cholesterol from atherosclerotic plaques and transports it to the liver for excretion in the bile. Consequently, higher levels of HDL are associated with a lower risk of IHD.

Understandably, dietary and pharmacologic approaches that lower LDL or total serum cholesterol have attracted considerable interest. High dietary intake of cholesterol and saturated fats (present in egg yolks, animal products, and certain oils) raises plasma cholesterol levels. Conversely, diets low in cholesterol and/or with higher ratios of polyunsaturated to saturated fats lower cholesterol levels. Omega-3 fatty acids (abundant in fish oils) are beneficial, whereas (*trans*)unsaturated fatty acids (used in baked goods and margarine) adversely affect cholesterol levels. Consumption of ethanol both raises HDL levels, whereas obesity and smoking lower it. *Statins* are a class of drugs that lower cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis.

#### Hypertension

*Hypertension* (see below) is another major risk factor for atherosclerosis; both systolic and diastolic blood pressure can increase the risk of IHD by approximately 60% in comparison with normotensive individuals. In roughly half of hypertensive patients will die of IHD or congestive heart failure, and another third will develop left ventricular hypertrophy in many cases probably represents a marker of long-standing functional hypertension.

#### Cigarette Smoking

*Cigarette smoking* is a well-established risk factor in men, and an increase in the number of women who smoke is increasing incidence and severity of atherosclerosis in women. Prolonged (years) smoking of one pack per day increases the death rate from IHD by 200%. Smoking cessation reduces that risk substantially.

#### Diabetes Mellitus

*Diabetes mellitus* induces hypercholesterolemia (see Chapter 20) as well as a markedly increased risk of IHD. When all other factors being equal, the incidence of myocardial infarction is twice as high in diabetic as in nondiabetic individuals. Diabetes also increases the risk of strokes and a 100-fold increased risk of atherosclerosis-induced gangrene of the lower extremities.

### Additional Risk Factors for IHD

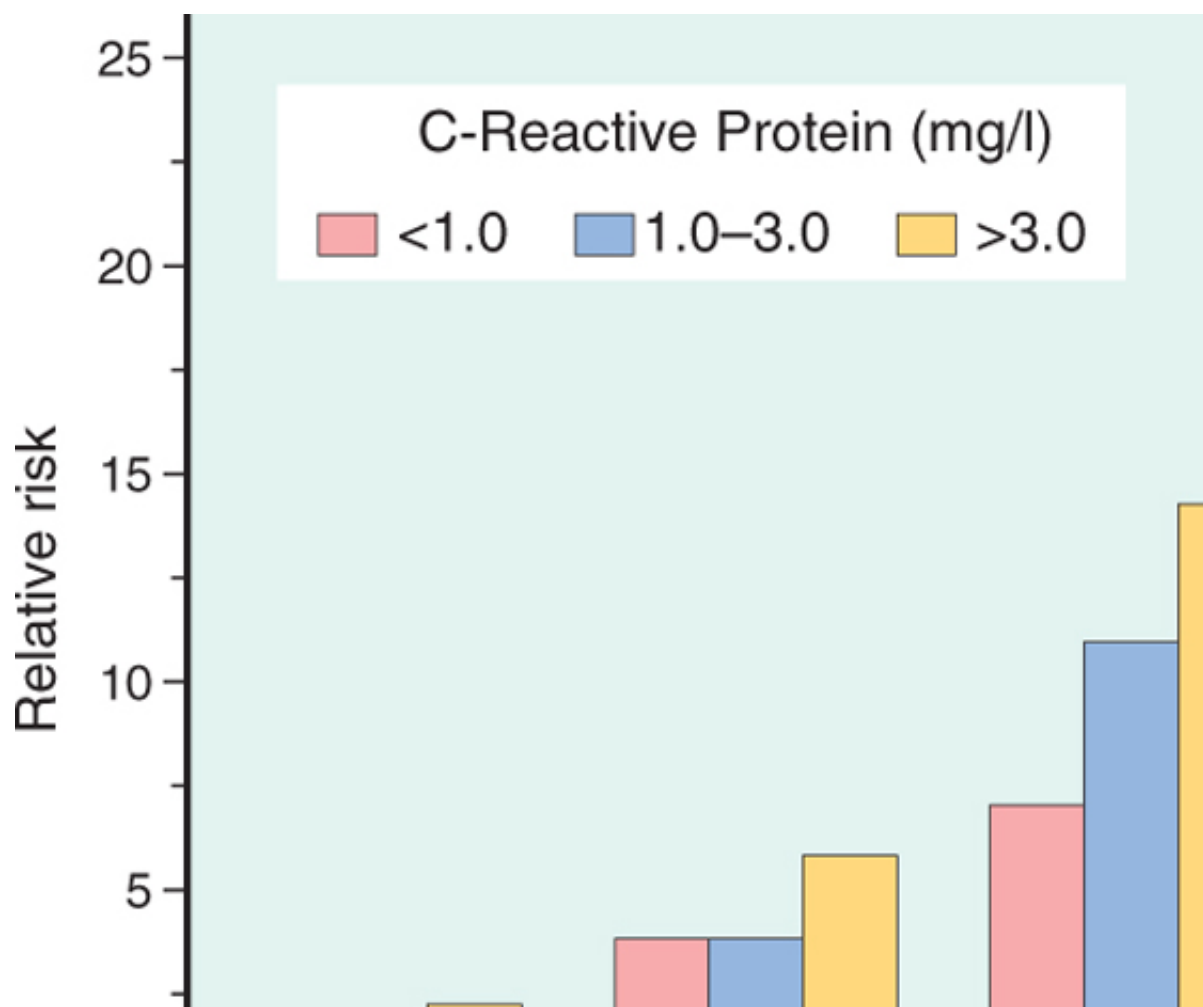
Despite the identification of hypertension, diabetes, smoking, and hyperlipidemia as major risk factors, cardiovascular events occur in the absence of any of these. Indeed, even though hyperlipidemia is a major risk factor, cardiovascular events in previously healthy women occurred with LDL cholesterol levels below 160 mg/dL (which would connote low risk). Clearly, other "nontraditional" factors contribute to risk; the assessment of some of these is the subject of ongoing research.

#### *Inflammation as marked by C-reactive protein*

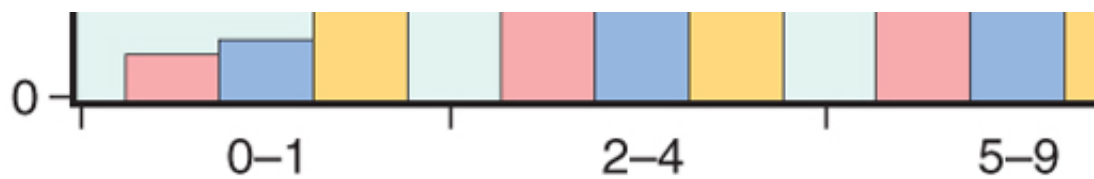
Inflammation is present during all stages of atherogenesis and is intimately linked with atherosclerosis (see below). With the increasing recognition that inflammation does play a significant causal role in IHD, the measurement of CRP has become important in overall risk stratification. While a number of systemic markers of inflammation (including interleukin-6 [IL-6], soluble intercellular adhesion molecule-1, CD40 ligand, etc.), C-reactive protein (CRP) is the cheapest and most sensitive.

CRP is an acute-phase reactant synthesized primarily by the liver. It is downstream of a number of cytokines in the innate immune response by opsonizing bacteria and activating complement (Chapter 5). In atherosclerotic intima, it can also regulate local endothelial adhesion and thrombotic states. Most studies predict the risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death in healthy individuals (Fig. 10-5). Interestingly, although there is no direct evidence that lowering CRP reduces cardiovascular risk, weight loss, and exercise all reduce CRP; moreover, statins reduce CRP levels largely independent of their effect on cholesterol.

#### *Hyperhomocystinemia*







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Figure 10-5 CRP adds prognostic information at all levels of traditional risk identified from the Framingham Heart Study. The x-axis is the 10 year risk of a cardiovascular event derived from the Framingham study. In each group of Framingham risk, CRP values further stratify the patients. For example, if a patient has a high CRP value, his likelihood of developing a cardiovascular event is actually less than a patient in the lower risk group with high CRP. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular event. Copyright © 2002 Massachusetts Medical Society. All rights reserved.

Clinical and epidemiologic studies show a strong relationship between total serum homocysteine levels and peripheral vascular disease, stroke, and venous thrombosis. Elevated homocysteine levels can be caused by low folate intake, although the jury is still out on whether supplemental folate and vitamin B<sub>6</sub> ingestion can reduce the risk of disease. *Homocystinuria*, due to rare inborn errors of metabolism, results in elevated levels of circulating homocysteine and premature vascular disease.

#### *Lipoprotein a*

*Lipoprotein a*, or *Lp(a)*, is an altered form of LDL that contains the apolipoprotein B-100 portion of LDL. High levels of *Lp(a)* are associated with a higher risk of coronary and cerebrovascular disease, independent of other risk factors.

#### *Factors Affecting Hemostasis*

Several markers of hemostatic and/or fibrinolytic function (e.g., elevated plasminogen activator inhibitor-1) are associated with major atherosclerotic events, including myocardial infarction and stroke. The increased risk of ischemic events with selective cyclooxygenase 2 (COX-2) inhibitors is believed to be due to suppression of endothelium-derived nitric oxide and platelet-derived thromboxane A<sub>2</sub>, thus creating a prothrombotic state.

#### *Other Factors*

Factors associated with a less pronounced and/or difficult-to-quantitate risk include lack of exercise, smoking, personality; and obesity (the latter due to hypertension, diabetes, hypertriglyceridemia, and decreased HDL).

#### **Pathogenesis**

The overwhelming clinical importance of atherosclerosis has stimulated enormous efforts to understand its pathogenesis. The model of atherosclerosis expressed by the *response-to-injury hypothesis*. This model views *atherosclerosis as a response to injury of the arterial wall to endothelial injury. Lesion progression occurs through interactions of modified lipoproteins, macrophages, T lymphocytes, and the normal cellular constituents of the arterial wall (Fig. 10-6).*

*Chronic endothelial injury*, with resultant endothelial dysfunction, causing (among other things) increased permeability to lipoproteins, platelet adhesion, and thrombosis. *Accumulation of lipoproteins* (mainly LDL and its oxidized forms) in the *endothelium*, followed by migration into the intima and transformation into *macrophages*. *Macrophages* release from activated platelets, macrophages, and vascular wall cells, inducing *SMC recruitment* and *SMC proliferation and ECM production*. *Lipid accumulation* both extracellularly and within *SMCs*.

The accumulation of lipid-containing macrophages in the intima gives rise to "fatty streaks" (Fig. 10-6, step 1). The progression to a fibrofatty atheroma (Fig. 10-6, step 5) consisting of proliferated SMC, foam cells, extracellular lipid, and collagen. Atherosclerosis will now be considered in detail.

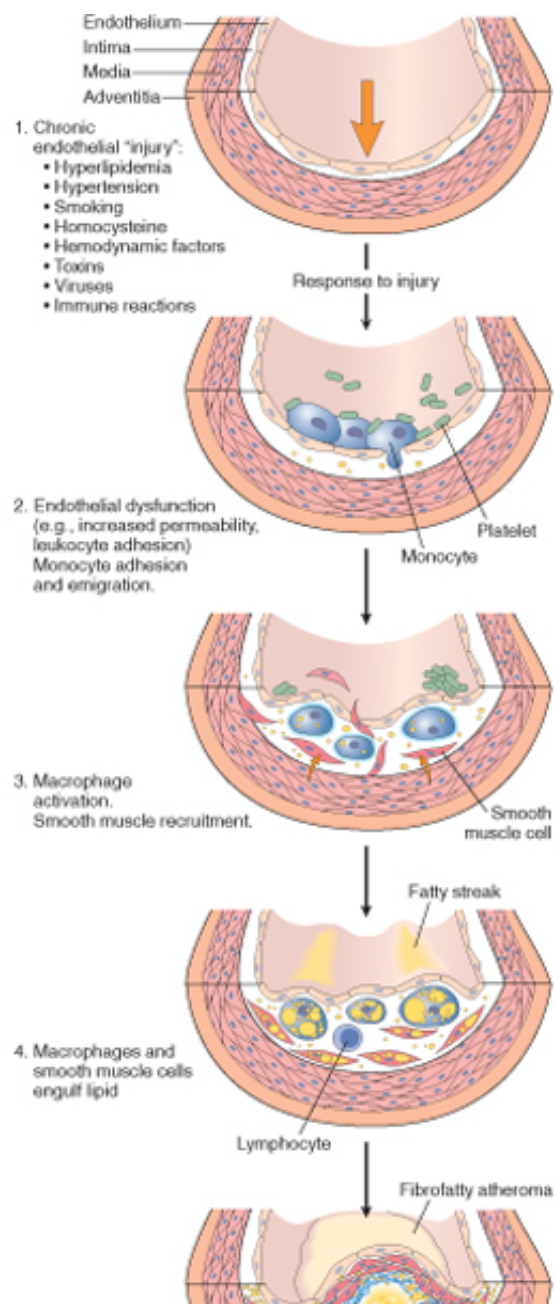
#### **Endothelial Injury**

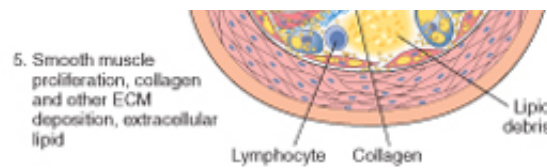
## Endothelial injury

Chronic or repetitive endothelial injury is the cornerstone of the response-to-injury hypothesis. Endothelial injury, whether induced experimentally by mechanical denudation, hemodynamic forces, immune complex deposition, or results in intimal thickening; in the presence of high-lipid diets, typical atheromas ensue. However, *morphologically intact endothelium*. Thus, non-denuding *endothelial dysfunction* underlies human atherosclerosis. In the presence of dysfunctional ECs there is increased endothelial permeability, enhanced leukocyte adhesion,

The specific causes of endothelial dysfunction in early atherosclerosis are not completely understood. Factors such as cigarette smoke, homocysteine, and even infectious agents. Inflammatory cytokines (e.g., tumor necrosis factor) increase the expression of pro-atherogenic genes in EC. Nevertheless, the two most important causes of endothelial dysfunction are shear stress disturbances and hypercholesterolemia. Inflammation is also an important contributor.

## Hemodynamic Disturbance





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Figure 10-6 Evolution of arterial wall changes in the response to injury hypothesis. **1.** Normal. **2.** Endothelial injury (latter to sites where endothelium has been lost). **3.** Migration of monocytes and SMCs into the intima. **4.** SMC proliferation and collagen deposition, extracellular lipid. **5.** Well-developed plaque.

The importance of hemodynamic turbulence in atherogenesis is illustrated by the observation that vessels, branch points, and along the posterior wall of the abdominal aorta, where there are disturbed flow patterns. These sites demonstrate that nonturbulent laminar flow in other parts of the normal vasculature leads to the inhibition of atherosclerosis (e.g., the antioxidant superoxide dismutase) actually *protect* against atherosclerosis. Such observations support the nonrandom localization of early atherosclerotic lesions.

### Lipids

Lipids are typically transported in the bloodstream bound to specific apoproteins (forming lipoproteins). Genetic defects that result from mutations that encode defective apoproteins or alter the lipoprotein receptors on cells, that affects the circulating levels of lipids (e.g., nephrotic syndrome, alcoholism, hypothyroidism, and certain abnormalities in the general population (indeed, present in many survivors of myocardial infarction) include (1) decreased HDL cholesterol levels, and (2) increased levels of the abnormal Lp(a) (see

The evidence implicating hypercholesterolemia in atherogenesis includes the following observations:

The dominant lipids in atheromatous plaques are cholesterol and cholesterol esters. Genetic defects in lipid metabolism that cause hyperlipoproteinemia are associated with accelerated atherosclerosis. Familial hypercholesterolemia, caused by defective LDL receptors and inadequate hepatic LDL uptake, leads to premature atherosclerosis and myocardial infarction before the age of 20 years. Similarly, accelerated atherosclerosis occurs in animals with defects in apolipoproteins or LDL receptors. Other genetic or acquired disorders (e.g., diabetes mellitus, obesity, and certain abnormalities in the general population) lead to premature atherosclerosis. Epidemiologic studies demonstrate a strong correlation between the severity of atherosclerosis and the levels of total plasma cholesterol or LDL. Lowering serum cholesterol levels by diet or drugs slows the rate of progression of atherosclerosis, causes regression of some plaques, and reduces the risk of atherosclerotic complications.

The mechanisms by which hyperlipidemia contributes to atherogenesis include the following:

Chronic hyperlipidemia, particularly hypercholesterolemia, can directly impair EC function by increasing the production of oxygen species. Among other effects, oxygen free radicals accelerate nitric oxide<sub>Rx</sub> decay, thereby increasing local shear stress. With chronic hyperlipidemia, lipoproteins accumulate in the vessel wall and become oxidized through the action of oxygen free radicals locally generated by macrophages or ECs. Oxidized LDL stimulates the release of growth factors, cytokines, and chemokines by ECs and macrophages through a *scavenger receptor*, distinct from the LDL receptor (Chapter 7), resulting in increased recruitment into lesions. Finally, oxidized LDL is cytotoxic to ECs and SMCs and can induce apoptosis. The role of oxidized LDL in atherogenesis is suggested by its accumulation within macrophages at all sites of atherosclerosis. Antioxidant therapy (β-carotene and vitamin E<sub>Rx</sub>) protects against atherosclerosis in animal models and is effective for preventing IHD.

### Inflammation

Inflammatory cells and mediators are involved in the initiation, progression, and the complications of atherosclerosis. In normal vessels do not bind inflammatory cells, early in atherogenesis dysfunctional arterial ECs express adhesion molecules that encourage leukocyte adhesion; vascular cell adhesion molecule 1 (VCAM-1) in particular binds to leukocytes. When leukocytes adhere to the endothelium, they migrate into the intima under the influence of locally produced chemokines.

Monocytes transform into macrophages and avidly engulf lipoproteins, including oxidized LDL. This process of differentiation into macrophages (and ultimately into foam cells) is theoretically protective, as it removes harmful lipid particles. Over time, however, progressive accumulation of oxidized LDL drives macrophage activation (via oxidized LDL or T cells, see below) results in cytokine production (e.g., TNF- $\alpha$ ), adhesion and chemokine production that in turn propel mononuclear inflammatory cell recruitment. Macrophages produce reactive oxygen species, aggravating LDL oxidation. T lymphocytes recruited to the site can generate a chronic immune inflammatory state. It is not clear whether the T cells are recruited by bacterial or viral antigens, heat-shock proteins [see below], or modified arterial wall constituents. Nevertheless, activated T cells in turn produce inflammatory cytokines, (e.g., interferon- $\gamma$ ), which in turn can stimulate macrophages as well as endothelial cells. Of the chronic inflammatory state, activated leukocytes and vascular wall cells release growth factors and ECM synthesis.

### Infection

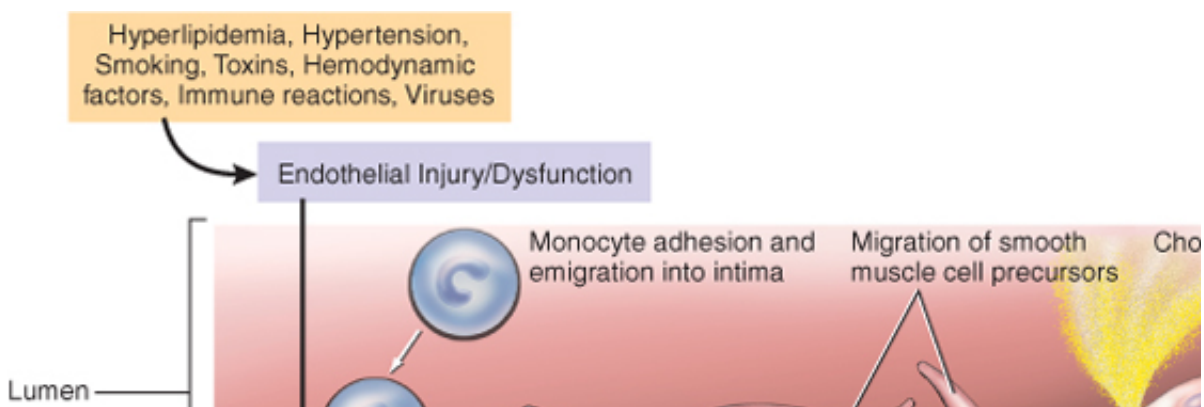
Although there is tantalizing evidence that infections may drive the local inflammatory process that leads to atherosclerosis, this hypothesis has yet to be definitively proven. Herpesvirus, cytomegalovirus, and *Chlamydia pneumoniae* are found in atherosclerotic plaque but not in normal arteries, and seroepidemiologic studies find increased antibody titers with more severe atherosclerosis. However, a causal link between any of these infections and the development of atherosclerosis remains to be established.

### Smooth Muscle Proliferation

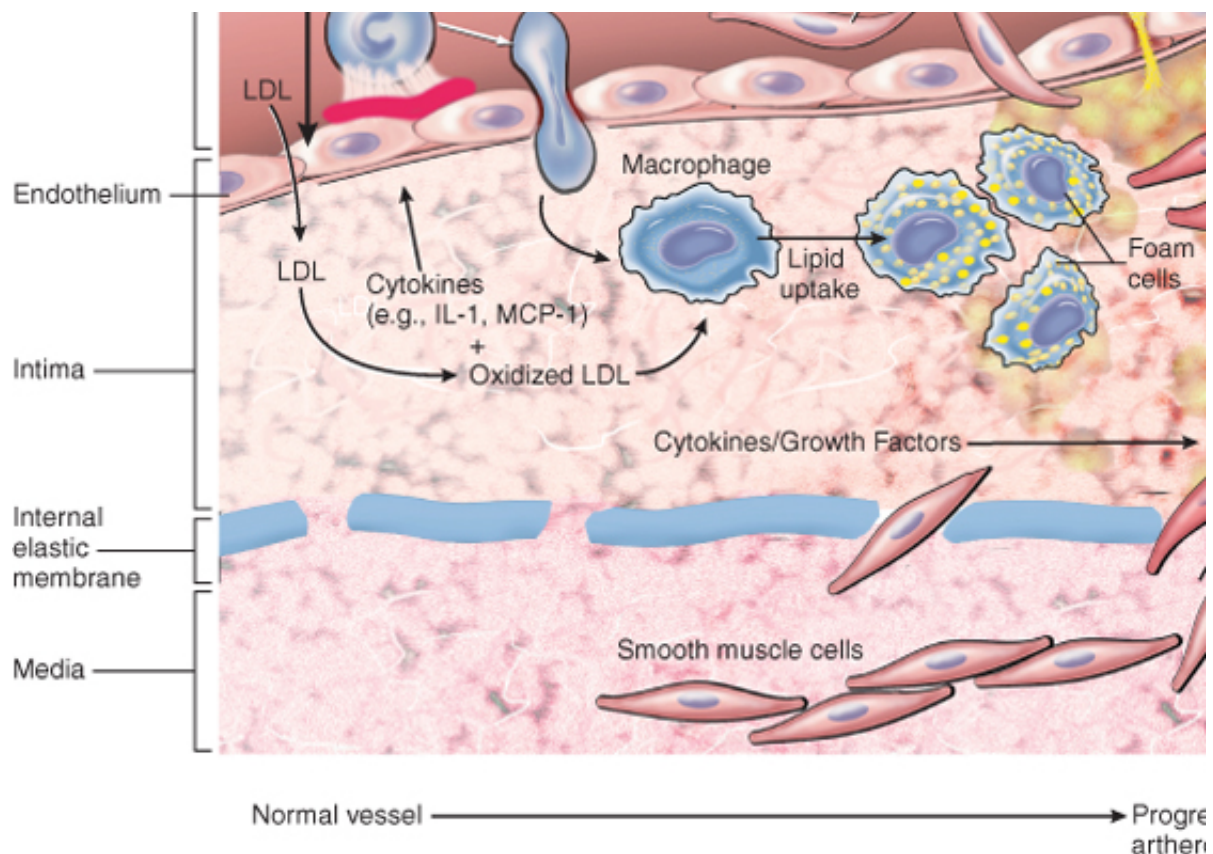
Intimal SMC proliferation and ECM deposition convert a fatty streak into a mature atheroma (see below). This is the progressive growth of atherosclerotic lesions. Recall that the intimal SMCs have a proliferative capacity unlike the underlying medial SMCs and, in fact, may substantially derive from the recruitment of circulating SMCs. Factors implicated in SMC proliferation and ECM synthesis, including platelet-derived growth factor (PDGF) as well as by macrophages, ECs, and SMCs), fibroblast growth factor, and transforming growth factor- $\beta$  (TGF- $\beta$ ) stimulate ECM (notably collagen), which stabilizes atherosclerotic plaques. However, activated inflammatory cells also promote SMC apoptosis, and they also increase ECM catabolism, resulting in unstable plaques.

*Figure 10-7 summarizes the major proposed cellular mechanisms of atherogenesis, emphasizing the role of inflammation. This scheme highlights the canon that atherosclerosis is a chronic inflammatory response to various insults, including endothelial injury, lipid accumulation and oxidation, and thrombosis. Atheromas are composed of dysfunctional ECs, recruited and proliferating SMCs, and admixed chronic inflammation (macrophages, T cells, and other immune cells) that contribute mediators that influence atherogenesis. At early stages, intimal plaques are little more than a collection of foam cells, some of which die, releasing lipid and necrotic debris. With progression, the atheroma becomes more complex, with proteoglycans synthesized by SMCs; connective tissue is particularly prominent on the intimal aspect. Typically, atheromas retain a central core of lipid-laden cells and fatty debris that may also become calcified or thrombotic. A superimposed thrombus is often associated with catastrophic clinical events.*

With this overview of pathogenesis we can now discuss the morphologic evolution and correlates







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 Figure 10-7 Hypothetical sequence of cellular interactions in atherosclerosis. Hyperlipidemia and other risk factors lead to adhesion of platelets and monocytes and release of growth factors, including platelet-derived growth factor, which promotes proliferation. Foam cells of atheromatous plaques are derived from both macrophages and SMCs—from macrophages via the scavenger receptor and low-density lipoprotein (LDL) modifications recognized by scavenger receptors (e.g., oxidized LDL). Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia. Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux, and high-density lipoprotein (HDL) promotes efflux. SMCs migrate to the intima, proliferate, and produce ECM, including collagen.

## Morphology

**Fatty Streaks.** Fatty streaks are composed of lipid-filled foam cells but are not significant lesions. They do not cause any disturbance in blood flow. They begin as multiple minute yellow spots that coalesce into elongated streaks, 1 cm long or longer (Fig. 10-8). Fatty streaks can be found in infants younger than 1 year and are present in virtually all children older than 10 years. Their distribution is independent of geography, race, sex, or environment. Coronary fatty streaks begin to form in adolescence at anatomic sites that later tend to develop plaques. The relationship of fatty streaks to atherosclerosis is uncertain; although they may evolve into precursors of plaques, not all fatty streaks become advanced atherosclerotic lesions.

**Atherosclerotic Plaque.** The key processes in atherosclerosis are intimal thickening and plaque formation (see Figs. 10-3 and 10-7). Atheromatous plaques (also called fibrous or fibrofatty plaques) protrude into the lumen of the artery and grossly appear white to yellow; thrombosis superimposed on ulcerated plaques is red-brown in color. Plaques vary from 0.3 to 1.5 cm in diameter and can form large masses (Fig. 10-9).

Atherosclerotic lesions are patchy, usually involving only a portion of any given artery section, the lesions therefore appear "eccentric" (Fig. 10-10A). The focality of atherosclerosis, despite the uniform exposure of vessel walls to such factors as cigarette smoke toxins, elevated blood pressure, and hyperglycemia—is almost certainly due to the vagaries of vascular hemodynamics. In



such as turbulence at branch points, leads to certain portions of a vessel wall being plaque formation. Although focal and sparsely distributed at first, atherosclerotic lesions become numerous and more diffuse with time.

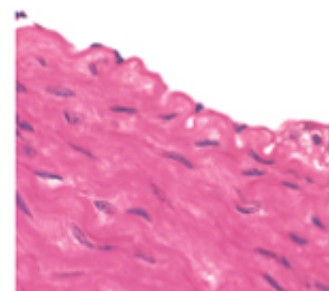
In humans, the abdominal aorta is typically much more frequently involved than the descending aorta. **the most extensively involved vessels are the lower abdominal aorta, the popliteal arteries, the internal carotid arteries, and the vessels of the upper extremities.** Vessels of the upper extremities are usually spared, as are the mesenteric and renal arteries. Nevertheless, in an individual case, the severity of atherosclerosis in one artery can be severe, while in another it is mild. Moreover, in any given vessel, lesions at various stages often coexist.

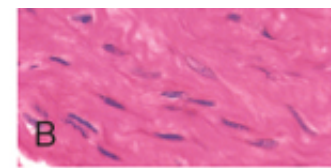
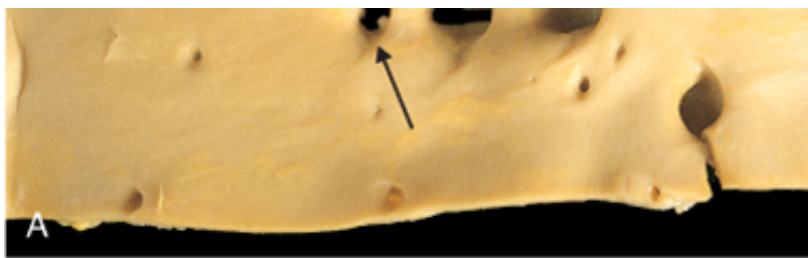
**Atherosclerotic plaques have three principal components: (1) cells, including macrophages and T cells; (2) ECM, including collagen, elastic fibers, and proteoglycans; and (3) extracellular lipid (Fig. 10-10).** These components occur in varying proportions in different lesions. Typically, the superficial **fibrous cap** is composed of SMCs and fibroblasts. Beneath and to the side of the cap (the **"shoulder"**) is a more cellular area containing many macrophages and SMCs. Deep to the fibrous cap is a **necrotic core**, containing lipid (primarily cholesterol esters), debris from dead cells, foam cells (lipid-laden macrophages and SMCs), fibrin, thrombus, and other plasma proteins; the cholesterol content is frequently present in the form of cholesterol crystals that are washed out during routine tissue processing and leave behind only empty spaces. In the early lesions, there is usually **neovascularization** (proliferating small blood vessels) within the plaque. Some plaques ("fibrous plaques") are composed primarily of SMCs and fibrous tissue.

Plaques generally continue to change and progressively enlarge through cell death, matrix synthesis and degradation (remodeling) of ECM, and organization of thrombi. More advanced lesions undergo **calcification** (Fig. 10-10C). Patients with advanced coronary calcification are at high risk for coronary events.

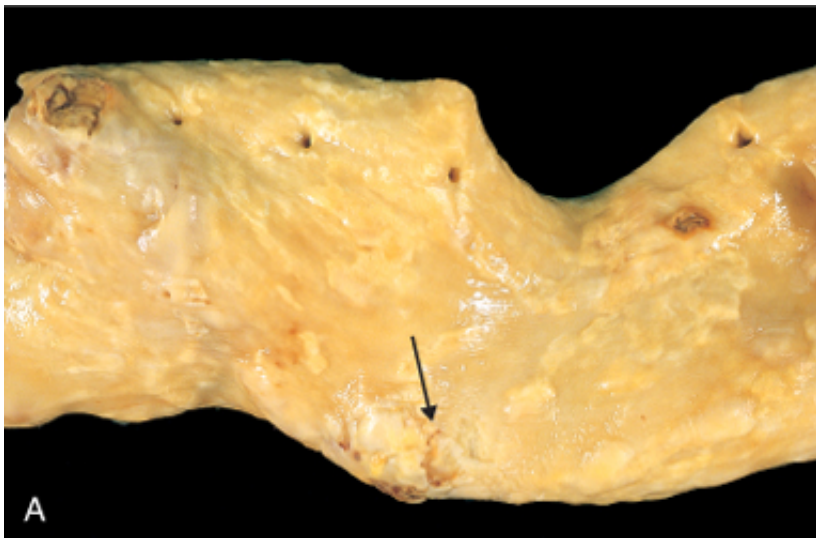
Atherosclerotic plaques are susceptible to the following pathologic changes with clinical significance:

**Rupture, ulceration, or erosion** of the luminal surface of atheromatous plaques exposes the thrombogenic substances in the plaque to the bloodstream and induces thrombus formation. Thrombi may partially or completely occlude the lumen and lead to downstream ischemia (Fig. 10-11). If the patient survives the initial vascular occlusion, thrombi may become organized and incorporated into the growing plaque. **Hemorrhage** into a plaque. Rupture of the fibrous cap or of the thin-walled vessels in the areas of neovascularization can cause intraplaque hemorrhage; a contained hematoma may expand the plaque or induce plaque rupture. **Atheroembolism.** Plaque rupture can discharge debris into the bloodstream, causing emboli composed of plaque contents. **Aneurysm formation.** Atherosclerosis can lead to ischemic atrophy of the underlying media, with loss of elastic tissue, causing dilation of the vessel wall and development of aneurysms that may rupture.





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 Figure 10-8 Fatty streak—a collection of foam cells in the intima. **A**, Aorta with fatty streaks (arrows), associated with hypercholesterolemia. **B**, Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal, macrophage infiltration. (Reprinted with permission from Myron I. Cybulsky, University of Toronto, Ontario, Canada.)



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 Figure 10-9 Gross views of atherosclerosis in the aorta. **A**, Mild atherosclerosis composed of fibrous plaques. **B**, Advanced atherosclerosis with complicated lesions, some of which have coalesced.

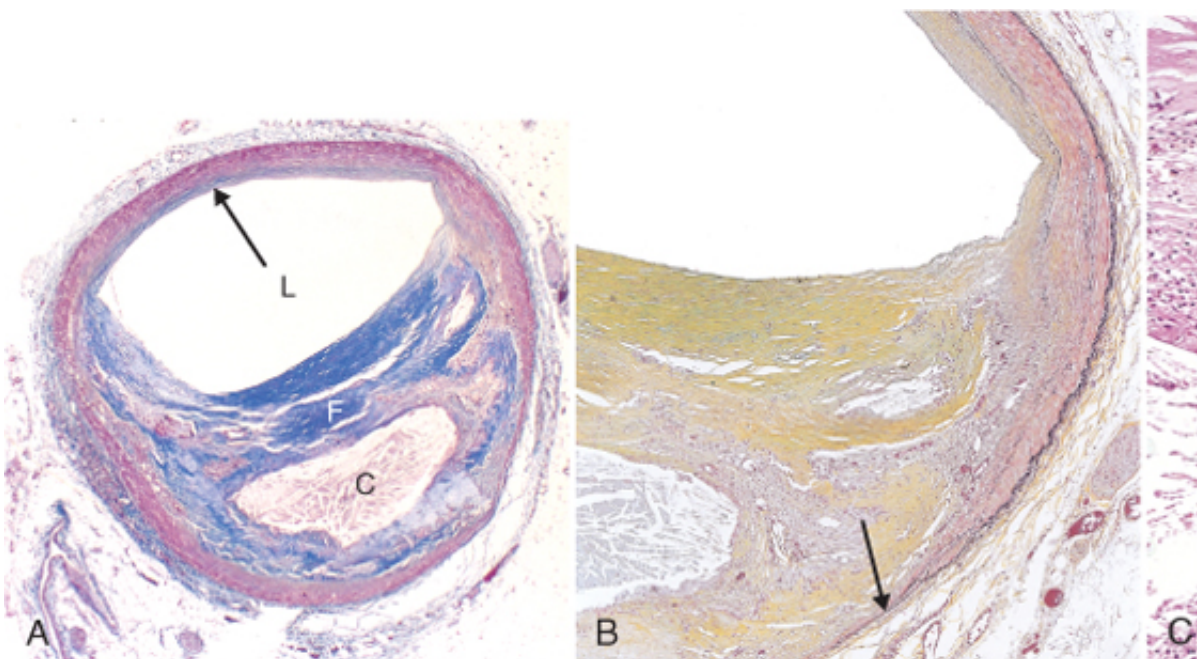


Figure 10-10 Histologic features of atheromatous plaque in the coronary artery. **A**, Overall architecture demonstrating a lipid core (C). The lumen (L) has been moderately narrowed. Note that a segment of the wall is plaque free (arrow). **B**, Higher power photograph of a section of the plaque demonstrating that the internal and external elastic membranes are destroyed and the media of the artery is thin. Higher magnification photomicrograph at the junction of the fibrous cap and core, showing scattered inflammatory cells and neovascularization (small arrows).

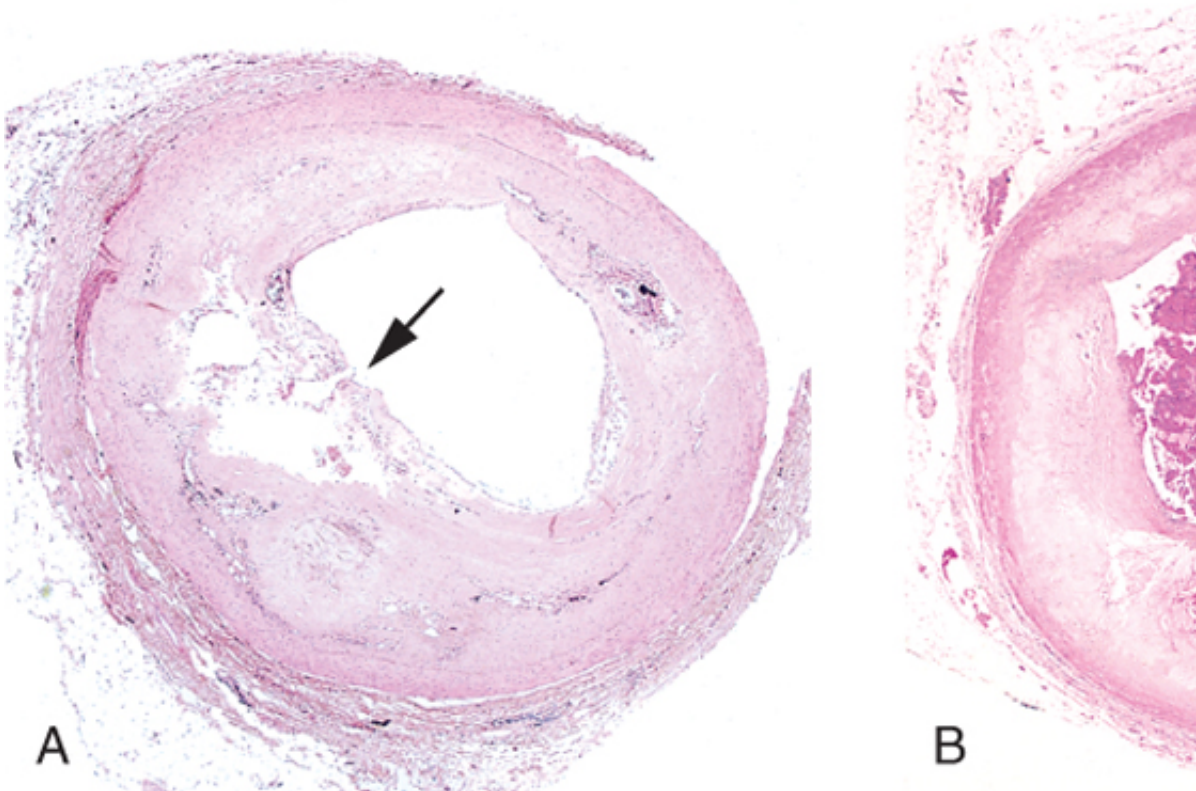


Figure 10-11 Atherosclerotic plaque rupture. **A**, Plaque rupture (arrow) without superimposed thrombus, in a p. **B**, Thrombosis superimposed on an atherosclerotic plaque with focal disruption of the fibrous cap (arrow), triggering t. Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles

### Natural History of Atherosclerosis

The natural history, morphologic features, and main pathogenic events of atherosclerosis are discussed in this section. Atherosclerosis primarily affects elastic arteries (e.g., aorta, carotid, and iliac arteries) and large arteries (e.g., coronary and popliteal arteries). In small arteries, atheromas can gradually occlude lumina, causing ischemic injury. Moreover, atherosclerotic plaques can undergo acute disruption and precipitate thrombosis. In large arteries, plaques are destructive, encroaching on the subjacent media and weakening the vessel wall, leading to aneurysms that can rupture. Moreover, atheromas can be friable, fragmenting into atheroemboli into distal vessels. *emphasize that atherosclerosis is a slowly evolving lesion usually requiring many decades to become clinically significant. However, rupture, thrombosis, or hematoma formation can rapidly precipitate clinical sequelae (Fig. 10-12).*

Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, and kidneys. The clinical consequences of atherosclerosis include myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease. Atherosclerosis also takes a toll through other consequences of impaired perfusion, such as mesenteric occlusion, sudden cardiac death, chronic IHD, and ischemic encephalopathy.



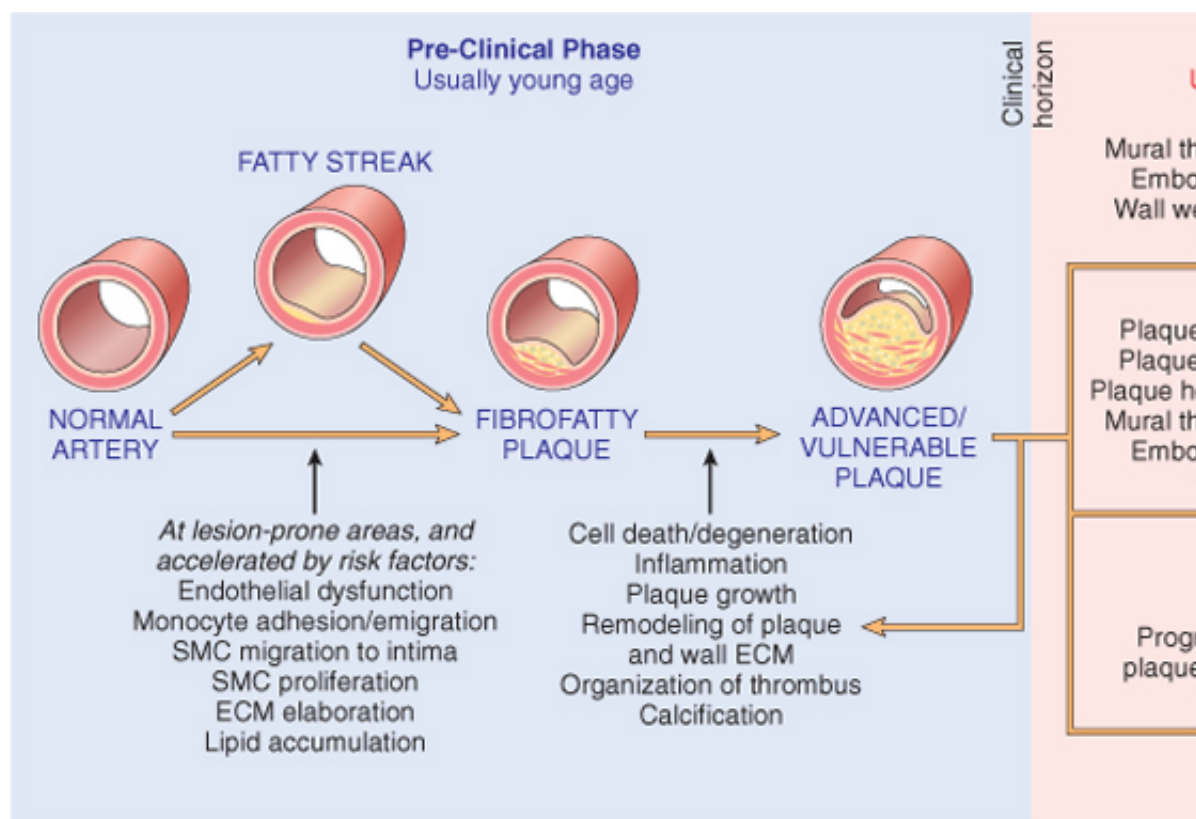
occlusion ultimately depend on arterial supply and tissue metabolic demand; details will be discussed in specific chapters.

## Prevention of Atherosclerotic Vascular Disease

Efforts to reduce the consequences and impact of atherosclerosis include

*Primary prevention* programs aimed at either delaying atheroma formation or encouraging persons who have not yet suffered a serious complication of atherosclerosis. *Secondary prevention* programs aimed at reducing the recurrence of events such as myocardial infarction or stroke in symptomatic patients

Primary prevention of atherosclerosis-related complications typically involves risk factor identification and intervention: cessation of cigarette smoking, control of hypertension, weight loss, exercise, and lowering of cholesterol levels while increasing HDL (e.g., by diet or through statins). Interestingly, statin use not only lowers cholesterol levels but also has a direct effect on the vascular wall. Several lines of evidence suggest that risk factor stratification and reduction is the most effective way to prevent atherosclerosis-related complications.



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Figure 10-12 The natural history, morphologic features, main pathogenic events, and clinical consequences of atherosclerosis.

Secondary prevention involves the judicious use of aspirin<sup>®</sup> (anti-platelet agent), statins, and beta-blockers, as well as surgical interventions (e.g., coronary artery bypass surgery, carotid endarterectomy). These interventions aim to reduce the risk of myocardial or cerebral events.

Considerable progress on the health impact of atherosclerosis-related disease has been made over the past few decades. Between 1963 (the peak year) and 2000 there has been an approximately 50% decrease in deaths from strokes, a reduction in mortality that alone has largely increased the life expectancy in the United States by 5 years. Three main contributors to this impressive improvement have been (1) prevention of risk factors and changes in life style (e.g., reduced cigarette smoking, reduced consumption of saturated fat and cholesterol), (2) improved methods of treatment of myocardial infarction and other complications of atherosclerosis, and (3) improved methods of treatment of hypertension and diabetes.

(2) improved methods of treatment of myocardial infarction and other complications of IHD; and (3) who have previously suffered serious atherosclerosis-related clinical events.

## **SUMMARY**

### **Atherosclerosis**

Atherosclerosis is an intima-based lesion organized into a fibrous cap and a (like) core and composed of SMCs, ECM, inflammatory cells, lipids, and nec is driven by an interplay of inflammation and injury to vessel wall cells. Many influence EC dysfunction, as well as SMC recruitment and stimulation. Ather slowly over decades but may acutely cause symptoms due to rupture, throm embolization. Risk factor recognition and reduction can reduce the incidence atherosclerosis-related disease.



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## HYPERTENSIVE VASCULAR DISEASE

Systemic and local blood pressure must be tightly regulated. Low pressures result in inadequate perfusion and/or tissue death. Conversely, high pressures that drive blood flow in excess of metabolic demands result in blood vessel and end-organ damage. Elevated blood pressure is called *hypertension*; as a result, it is a major risk factor for atherosclerosis. Here we will first discuss the mechanisms of normal blood pressure, then the factors that underlie hypertension, and finally the pathologic changes in vessels associated with hypertension.

Although hypertension is a common health problem with occasionally devastating outcomes, it typically has a long, asymptomatic course. Besides contributing to the pathogenesis of coronary heart disease and cerebrovascular disease, hypertension leads to cardiac hypertrophy and heart failure (*hypertensive heart disease*), aortic dissection, and renal failure. Despite our understanding of the molecular pathways that regulate normal blood pressure, the mechanisms of hypertension in many people remain unknown; consequently, we refer to most of these as "essential hypertension" (to name it).

Like height and weight, blood pressure is a continuously distributed variable, with essential hypertension being a deviation rather than a distinct entity. The detrimental effects of blood pressure increase continuously as the level of blood pressure distinguishes risk from safety. Nevertheless, a sustained diastolic blood pressure of 90 mm Hg or a sustained systolic pressure in excess of 140 mm Hg, constitutes hypertension; systolic blood pressure is more important in determining cardiovascular risk. By either criteria, some 25% of individuals in the United States are hypertensive. The prevalence and vulnerability to complications increase with age; they are also higher in African Americans. Treatment of hypertension dramatically reduces the incidence and death rates from IHD, heart failure, and stroke.

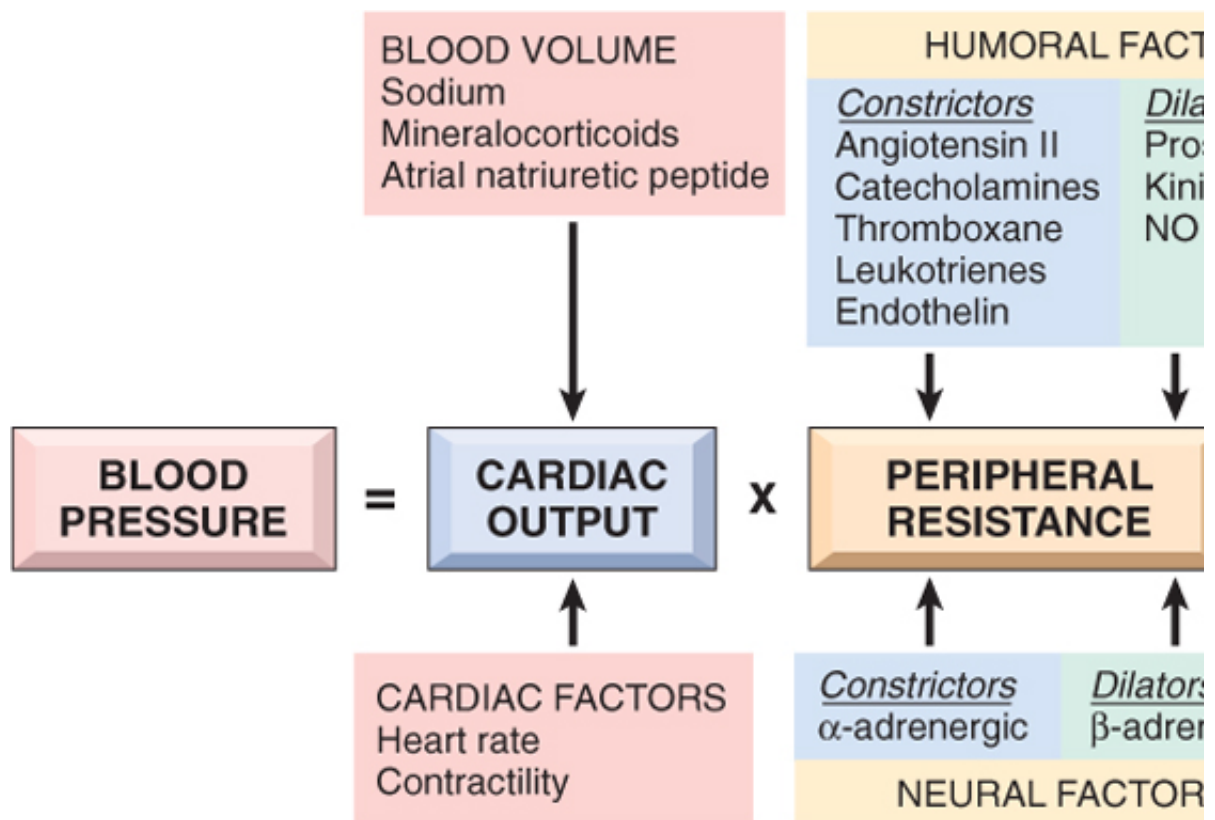
### Regulation of Blood Pressure

Blood pressure is a complex trait involving the interaction of multiple genetic and environmental factors. The major determinants are cardiac output and peripheral vascular resistance (Fig. 10-13). Cardiac output is affected by heart rate and stroke volume, which are in turn dependent on sodium concentrations. Peripheral resistance is regulated predominantly at the level of the small arteries and arterioles by neural and hormonal inputs. Normal vascular tone reflects an interplay between circulating factors (e.g., angiotensin II and catecholamines) and vasodilation (e.g., kinins, prostaglandins, and nitric oxide). Autoregulation, whereby increased blood flow induces vasoconstriction to protect tissues against ischemia, and myogenic autoregulation, whereby increased blood flow induces vasoconstriction to protect tissues against high pressure, are also involved. Finally, local factors, such as pH and hypoxia, as well as neural interactions ( $\alpha$ - and  $\beta$ -adrenergic systems), are also involved. The integrated response of these systems ensures adequate systemic perfusion, despite regional demand differences.

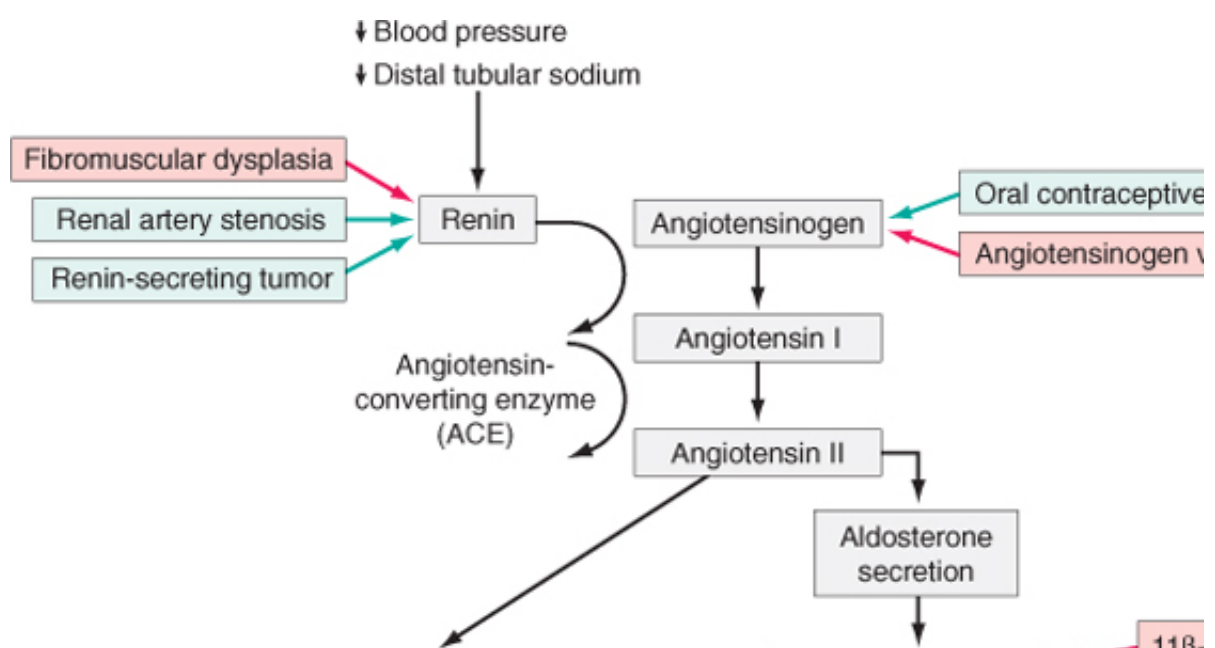
The kidneys (primarily) and adrenals (secondarily) are central players in blood pressure regulation. They regulate peripheral vessel tone and blood volume, as follows (Fig. 10-14):

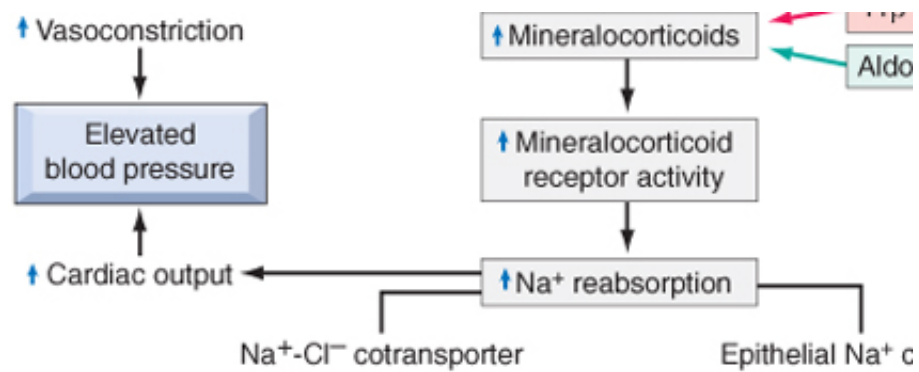
The *kidney* influences peripheral resistance and sodium homeostasis primarily through the renin-angiotensin system. The juxtaglomerular cells (modified myoepithelial cells) of the afferent arterioles produce the proteolytic enzyme renin when blood volume or pressure is reduced. Renin converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II raises blood pressure by: increasing peripheral resistance by inducing vasoconstriction; increasing blood volume by stimulating aldosterone secretion in the adrenals; increasing distal tubular reabsorption of sodium and water. The kidneys filter about 180 liters of plasma containing 23 moles of salt daily! Moreover, 99.5% of the filtered salt must be reabsorbed (assuming daily ingestion of only 100 mEq). As it turns out, the absorption of the last 2% of the filtered salt is critical for sodium homeostasis; this is regulated by the renin-angiotensin system acting on the epithelial  $\text{Na}^+$  channels. The kidney also produces a variety of vasorelaxant or antihypertensive substances (including prostaglandins and nitric oxide).

presumably counterbalance the vasopressor effects of angiotensin. When renal excretory pressure is a compensatory mechanism that can help restore fluid and electrolyte balance. Thus, *atrial natriuretic peptide*, secreted by heart atria (in heart failure) inhibits sodium reabsorption in distal tubules and causes global vasodilation



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Figure 10-13 Blood pressure modulation by effects on cardiac output and peripheral resistance





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 Figure 10-14 Blood pressure variation and the renin-angiotensin system. Components of the systemic renin-angiotensin system are indicated in red; arrows indicate sites of disorders that affect blood pressure by altering activity of this pathway are indicated in green. ENaC, epithelial sodium channel; EPO, erythropoietin; RAAS, renin-angiotensin-aldosterone system; RP: Molecular genetics of human blood pressure variation. Science 272:676-680, 1996.

## Pathogenesis of Hypertension

Table 10-3 lists the major causes of hypertension. *Ninety percent to 95% of hypertension is idiopathic and compatible with long life, unless a myocardial infarction, cerebrovascular accident, or other complication occurs.* The remainder of "benign hypertension" is secondary to renal disease or, less often, to narrowing of the aorta (atheromatous plaque (renovascular hypertension). Infrequently, hypertension is secondary to disorders such as primary aldosteronism, Cushing syndrome, pheochromocytoma, or other disorders.

About 5% of hypertensive persons show a rapidly rising blood pressure that if untreated leads to *accelerated* or *malignant hypertension*, the clinical syndrome is characterized by severe hypertension, renal failure, and retinal hemorrhages and exudates, with or without papilledema. It may develop in children and more often is superimposed on preexisting benign hypertension, either essential or secondary.

### Essential Hypertension

Even without knowing the specific lesion(s), it is reasonable to conclude that alterations in renal sodium excretion or structure underlie essential hypertension (Fig. 10-15). In established hypertension, both increased peripheral resistance and increased cardiac output contribute to the increased pressure.

*Reduced renal sodium excretion* in the presence of normal arterial pressure is probably a key common pathway for the pathogenesis of most forms of hypertension (see bottom of Fig. 10-15). If there is a cause for an obligatory increase in fluid volume and increased cardiac output, thereby elevating the blood pressure, enough additional sodium will be excreted by the kidneys to maintain the higher setting of blood pressure, enough additional sodium will be excreted by the kidneys to maintain the higher setting of blood pressure. Thus, a new steady state of sodium excretion would be achieved, but at the expense of higher blood pressure. *Vascular changes* may involve *functional vasoconstriction* or *changes in vascular resistance*. Chronic functional vasoconstriction could also conceivably result in permanent structural changes in the vessels.

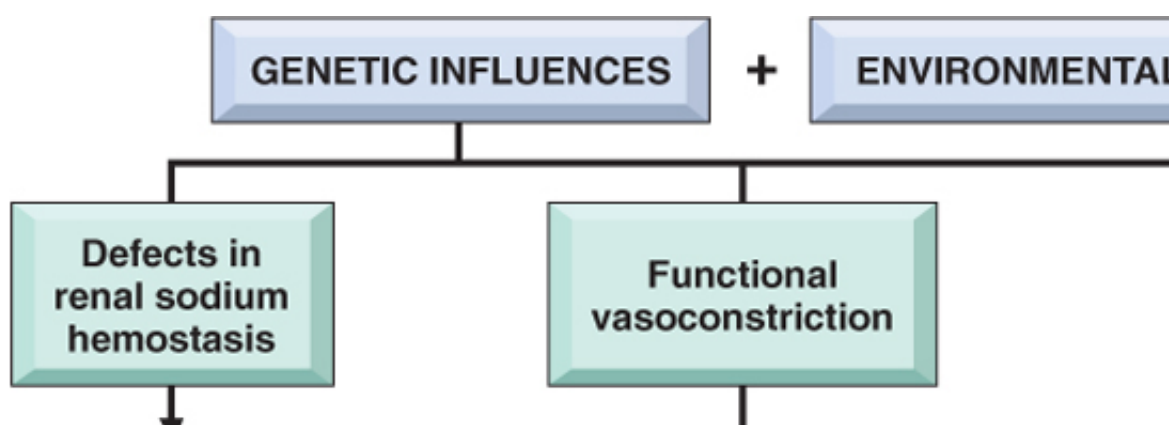
Table 10-3. Types and Causes of Hypertension (Systolic and Diastolic)

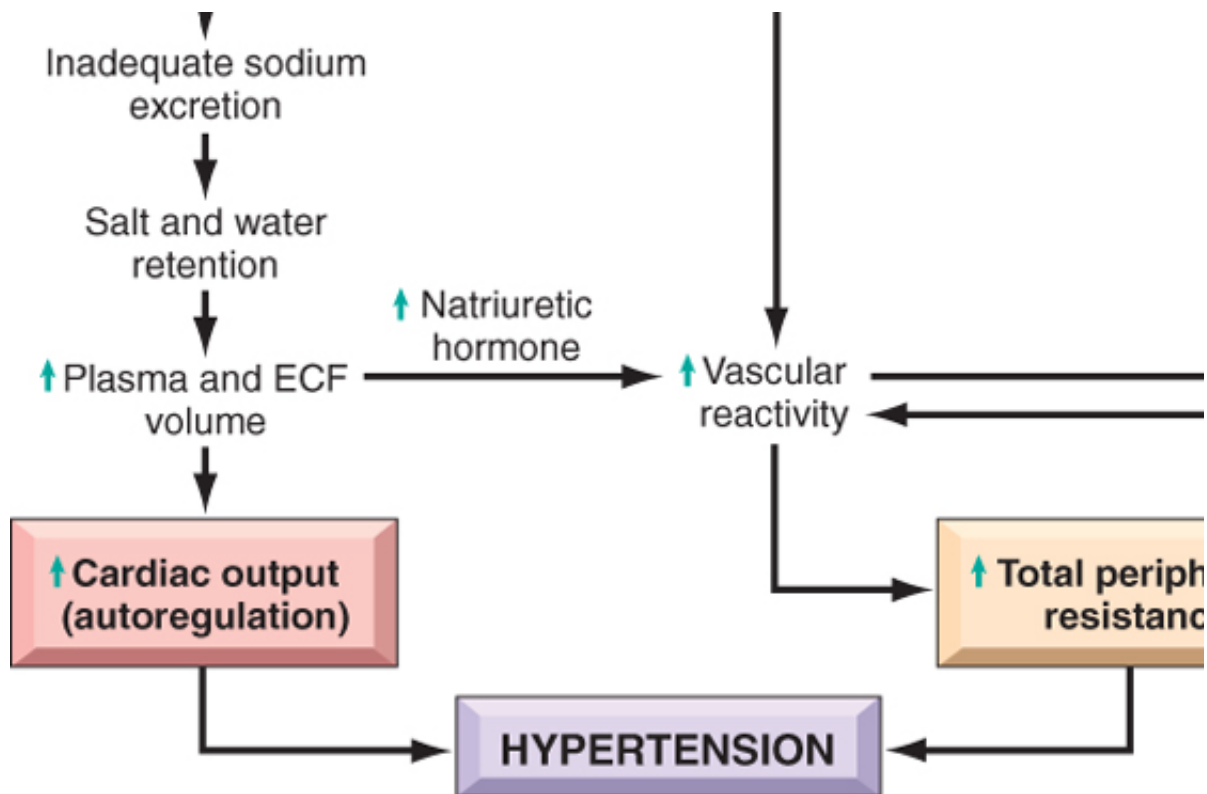
<b>Essential Hypertension (90% to 95% of Cases)</b>
<b>Secondary Hypertension</b>
<b>RENAL</b>
Acute glomerulonephritis
Chronic renal disease
Polycystic disease
Renal artery stenosis

Renal vasculitis
Renin-producing tumors
<b>ENDOCRINE</b>
Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia, I
Exogenous hormones (glucocorticoids, estrogen [including pregnancy-induced and oral contraceptives], s
containing foods, monoamine oxidase inhibitors)
Pheochromocytoma
Acromegaly
Hypothyroidism (myxedema)
Hyperthyroidism (thyrotoxicosis)
Pregnancy-induced
<b>CARDIOVASCULAR</b>
Coarctation of aorta
Polyarteritis nodosa
Increased intravascular volume
Increased cardiac output
Rigidity of the aorta
<b>NEUROLOGIC</b>
Psychogenic
Increased intracranial pressure
Sleep apnea
Acute stress, including surgery

Although we frequently cannot point to a discrete cause, the accepted wisdom is that essential hy multiple genetic and environmental factors affecting cardiac output and/or peripheral resistance.

*Genetic factors.* Studies comparing blood pressure in monozygotic and dizygotic twins, and hypertension, clearly establish a strong genetic component. Moreover, several single-gene hypertension (and hypotension) by altering net renal sodium resorption. Some of these are *Allelic variations in the genes encoding components of the renin-angiotensin system*. Hypo polymorphisms in both the angiotensinogen locus and the angiotensin II type I receptor loc angiotensin system may contribute to the known racial differences in blood pressure regula hypertension in the larger population are currently unknown but may well include genes tha sodium load, levels of pressor substances, reactivity of vascular SMCs to pressor agents, c modify the expression of any underlying genetic determinants of hypertension; stress, obe heavy consumption of salt are all implicated. Indeed, evidence linking dietary sodium intake different population groups is particularly impressive.





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 Figure 10-15 Hypothetical scheme for the pathogenesis of essential hypertension, implicating genetic defects in re-vascular tone, and structural regulation of vascular caliber. Environmental factors, especially increased salt intake resultant increase in cardiac output and peripheral resistance contributes to hypertension.

### Vascular Pathology in Hypertension

In addition to accelerating atherogenesis, hypertension-associated degenerative changes in the w- potentiate both aortic dissection and cerebrovascular hemorrhage. Hypertension is also associate disease: hyaline arteriosclerosis and hyperplastic arteriosclerosis (Fig. 10-16).

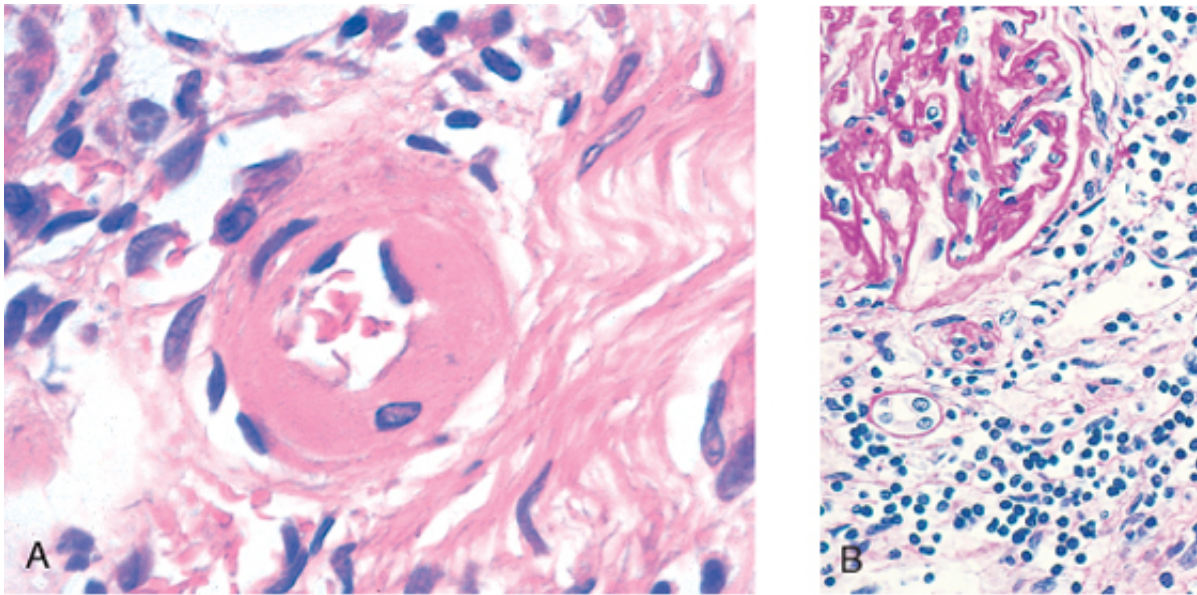
#### Morphology

**Hyaline Arteriosclerosis.** This vascular lesion consists of a homogeneous pink walls of arterioles with loss of underlying structural detail and with narrowing of the lumen. Encountered frequently in elderly patients, whether normotensive or hypertensive, is more generalized and more severe in patients with hypertension. It is also common characteristic microangiopathy in diabetes (Chapter 20).

The lesions reflect leakage of plasma components across vascular endothelium and production by SMCs secondary to the chronic hemodynamic stress of hypertension. Arteriosclerosis is a major morphologic characteristic of benign nephrosclerosis, in which narrowing causes diffuse impairment of renal blood supply, with loss of nephrons (Chapter 14).

**Hyperplastic Arteriosclerosis.** Related to more acute or severe elevations of blood pressure, hyperplastic arteriosclerosis is characteristic of (but not limited to) malignant hypertension (type II hypertension, over 120 mm Hg associated with acute cerebral and/or renal injury). Hyperplastic arteriosclerosis is associated with "onion-skin," concentric, laminated thickening of the walls of arterioles (Fig. 10-16B). The laminations consist of SMCs and thickened, duplicated basement membranes. In malignant hypertension, these hyperplastic changes are accompanied by fibrinoid deposits and necrotizing arteriolitis, particularly prominent in the kidney (Chapter 14).





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 Figure 10-16 Vascular pathology in hypertension. **A**, Hyaline arteriosclerosis. The arteriolar wall is hyalinized and arteriosclerosis (onion-skinning) causing luminal obliteration (arrow), with secondary ischemic changes, manifest in the upper left (periodic acid-Schiff stain). (Courtesy of Dr. Helmut Rennke, Brigham and Women's Hospital)

## SUMMARY

### Hypertension

Blood pressure is regulated by the combined influences of cardiac output (heart rate and stroke volume) and vascular resistance. Blood volume is dependent on renal sodium balance. Arteriolar vascular resistance is regulated by neural and hormonal inputs. Renin is secreted by the kidneys in response to reduced afferent stimulation of the juxtaglomerular apparatus or reduced glomerular filtration of sodium. Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II. Angiotensin II regulates blood pressure by increasing vascular smooth muscle contraction and by increasing aldosterone secretion to increase renal sodium resorption. Essential hypertension represents the most common form of hypertension and is a complex, multifactorial disorder resulting most likely from a combination of mutations or polymorphisms at several gene loci (e.g., sodium resorption system, aldosterone) in association with a variety of environmental influences. Secondary hypertension is caused by diseases of the kidneys or endocrine glands.



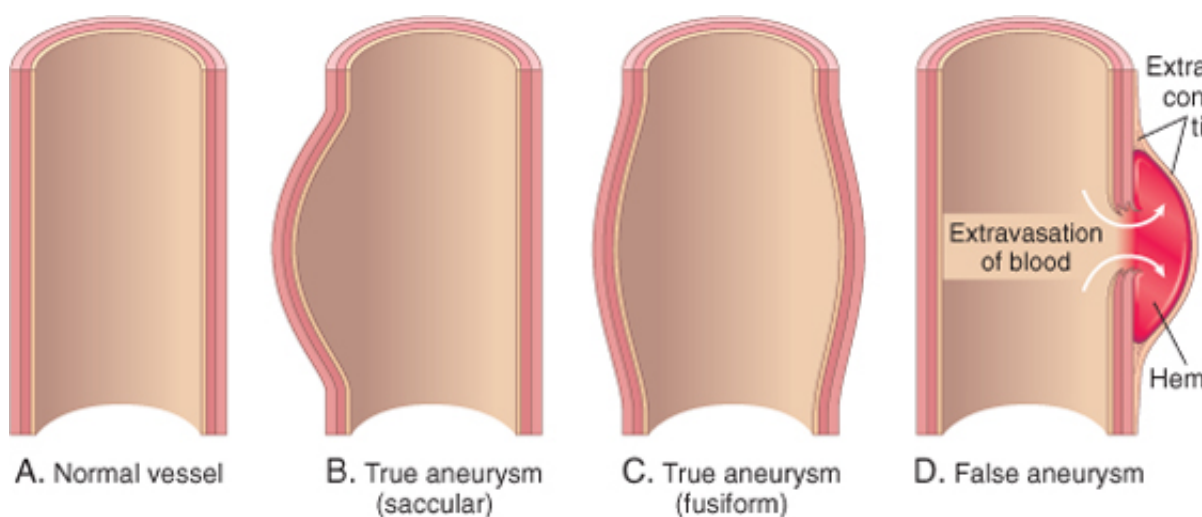
## ANEURYSMS AND DISSECTIONS

An *aneurysm* is a *localized abnormal dilation of a blood vessel or the heart* (Fig. 10-17). When an arterial wall (intima, media, and adventitia) or the attenuated wall of the heart, it is called a "true" aneurysm. Examples include congenital aneurysms, and ventricular aneurysms that follow transmural myocardial infarctions, and a *false aneurysm* (also called *pseudoaneurysm*) is a breach in the vascular wall leading to an extravascular space with the intravascular space ("pulsating hematoma"). Examples include ventricular ruptures after myocardial infarction, or a leak at the junction of a vascular graft with a natural artery. An *arterial dissection* is a tear in the wall of the artery, as a hematoma dissecting between its layers. Dissections are often but not always associated with aneurysms. Both true and false aneurysms as well as dissections can rupture, often with catastrophic consequences.

Descriptively, aneurysms are classified by macroscopic shape and size (see Fig. 10-17). *Saccular* aneurysms are outpouchings (involving only a portion of the vessel wall); they vary from 5 to 20 cm in diameter and are usually saccular. *Fusiform* aneurysms involve diffuse, circumferential dilation of a long vascular segment; they vary in diameter and are usually fusiform. Examples include extensive portions of the aortic arch, abdominal aorta, or even the iliacs. Particular aspects of shape and size are related to the underlying disease or clinical manifestations.

The two most important causes of aortic aneurysms are *atherosclerosis* and *cystic medial degeneration*. Other causes that weaken vessel walls and lead to aneurysms include trauma, congenital defects (e.g., *berry* aneurysms), or syphilis. Arterial aneurysms can also be caused by systemic diseases, such as vasculitis.

Infection of a major artery that weakens its wall is called a *mycotic aneurysm*; thrombosis and rupture of a mycotic aneurysm can originate (1) from embolization of a septic thrombus, usually as a complication of infection of a distant site; or (2) by circulating organisms directly infecting the arterial wall.



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Figure 10-17 Aneurysms. **A.** Normal vessel. **B.** True aneurysm, saccular type. The wall focally bulges outward and forms a sac. **C.** True aneurysm, fusiform type. There is circumferential dilation of the vessel, without rupture. **D.** False aneurysm. Blood has leaked out of the vessel (hematoma) that is bounded externally by adherent extravascular tissues. **E.** Dissection. Blood has entered the layers. Although this is shown as occurring through a tear in the intima, dissections can also occur by rupture of the media.

### Abdominal Aortic Aneurysm

Atherosclerosis, the most common cause of aneurysms, causes thinning and weakening of the media. Atherosclerotic plaques compress the underlying media and also compromise nutrient and waste diffusion from the lumen.

The media consequently undergoes degeneration and necrosis, thus allowing the dilation of the vessel wall. This process occurs most frequently in the abdominal aorta (*abdominal aortic aneurysm*, often abbreviated AAA), but the ascending and descending parts of the thoracic aorta can also be involved.

### Pathogenesis

AAA occurs more frequently in men and rarely develops before age 50. Atherosclerosis is a major contributor, since the incidence is less than 5% in men older than 60 years, despite almost universal atherosclerosis in that population. There can be a familial predisposition independent of any genetic predilection to atherosclerosis. In some cases, hereditary defects in structural components of the aorta can produce aneurysms (e.g., *Marfan syndrome*, a connective tissue disease that affects elastic tissue synthesis; see below).

In the majority of cases, however, AAA results from an altered balance of collagen degradation and synthesis, mediated by inflammatory infiltrates and the destructive proteolytic enzymes they produce and regulate. Thus, inadequate remodeling of these ECM components provides a background on which atherosclerosis develops. In this regard, matrix metalloproteinases (MMPs) have been increasingly implicated in AAA development. MMPs are produced by a variety of cells, including macrophages and T cells. These enzymes have the capacity to degrade virtually all components of the ECM in the arterial wall (collagen, elastin, and fibronectin). Concurrently, decreased levels of tissue inhibitor of metalloproteinases (TIMP) can also contribute to the pathogenesis of AAA.

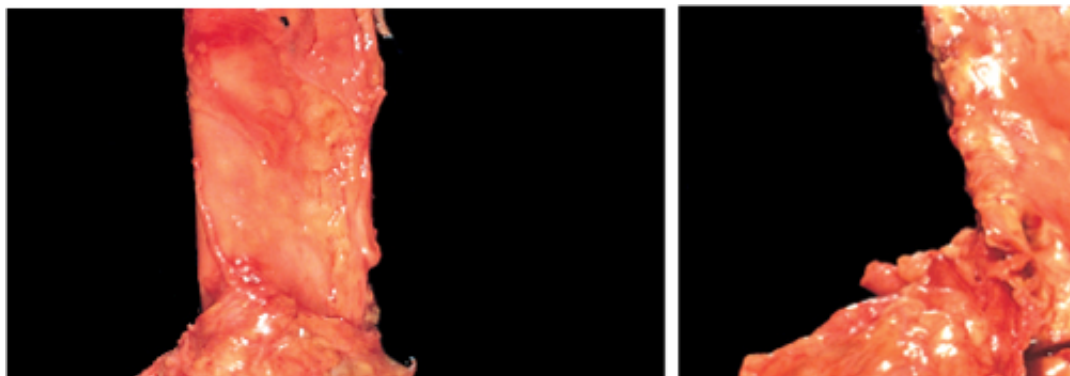
In this model of AAA pathogenesis, genetic predisposition may be related to the quality of the aortic wall, to TIMP polymorphisms, or to the nature of local inflammatory responses. Indeed, evidence suggests that cytokine environments shifted toward the production of T<sub>H</sub>2 cytokines (e.g., IL-4 and IL-10; [Chapter 10](#)) drive macrophages to produce increased amounts of elastolytic MMPs.

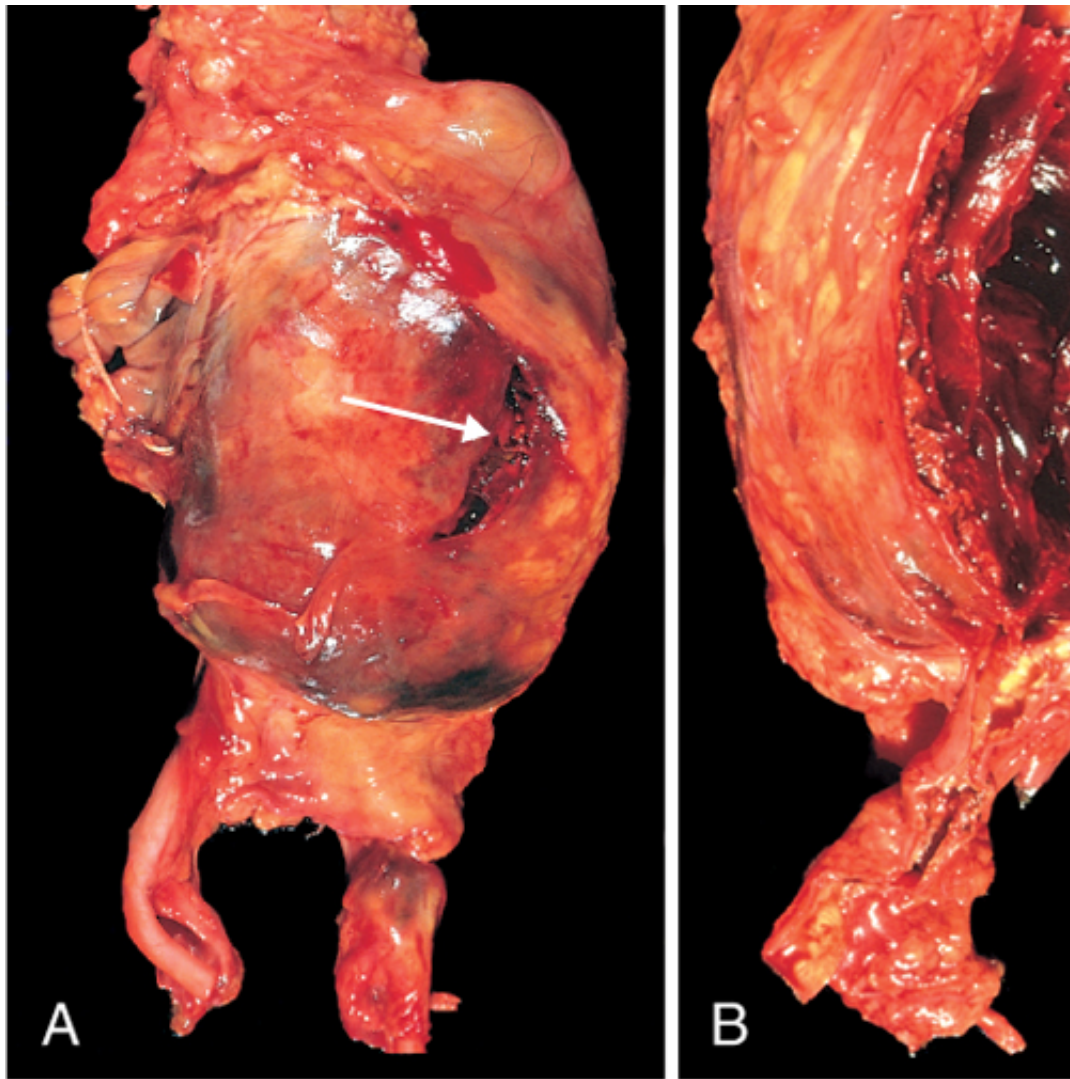
### Morphology

Usually positioned below the renal arteries and above the bifurcation of the aorta, the aneurysm is fusiform, as large as 15 cm in diameter, and as long as 25 cm ([Fig. 10-18](#)). There is extensive atherosclerosis with destruction and thinning of the underlying aortic media; the aneurysm contains a bland, laminated, poorly organized mural thrombus that may fill some or all of the aneurysm. Occasionally, the aneurysm can affect the renal and superior or inferior mesenteric arteries, producing direct pressure or by narrowing or occluding vessel ostia with mural thrombus. It is often accompanied by smaller aneurysms of the iliac arteries.

Two AAA variants merit special mention:

**Inflammatory AAAs** are characterized by dense periaortic fibrosis containing a lymphoplasmacytic infiltrate with many macrophages and often giant cells. The pathogenesis is uncertain. **Mycotic AAAs** are atherosclerotic lesions infected by lodging of bacteria in the wall, particularly in the setting of bacteremia from a primary *Salmonella* infection. In these cases, suppuration further destroys the media, potentiating rapid dilation and rupture.





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 Figure 10-18 Abdominal aortic aneurysm. **A**, External view, gross photograph of a large aortic aneurysm that ruptured; the rupture tract indicated by a probe. The wall of the aneurysm is exceedingly thin, and the lumen is filled by a large thrombus.

### *Clinical Course*

The clinical consequences of AAA include:

Rupture into the peritoneal cavity or retroperitoneal tissues with massive, potentially fatal hemorrhage resulting in downstream tissue ischemic injury—for example, iliac (leg), renal (kidney), mesenteric (intestine), vertebral (spinal cord) arteries  
 Embolism from atheroma or mural thrombus  
 Impingement on or erosion of adjacent structures (e.g., ureter or vertebrae)  
 Presentation as an abdominal mass (often palpably pulsatile)

The risk of rupture is directly related to the size of the aneurysm, varying from nil for AAAs of 4 cm to 11% per year for AAAs between 5 and 6 cm, and 25% per year for AAAs between 6 and 7 cm. Consequently, aneurysms of 5 cm or more in diameter are managed aggressively, usually by surgery. Timely surgery is critical; operative mortality for unruptured aneurysms is approximately 5%, whereas mortality for ruptured aneurysms carries a mortality rate of more than 50%. It is worth reiterating that because atherosclerosis is a systemic disease, it is also very likely to have atherosclerosis in other vascular beds and is at a significantly increased risk of rupture.

### ***Syphilitic Aneurysm***



The *obliterative endarteritis* (see below) characteristic of the tertiary stage of syphilis (lues) can involve the body. Involvement of the vasa vasorum of the aorta is particularly devastating; this results in ischemic dilation of the aorta and aortic annulus, and eventually valvular insufficiency. Fortunately, better results in early stages have made this a vanishingly rare complication in the U.S. and Western Europe.

### Morphology

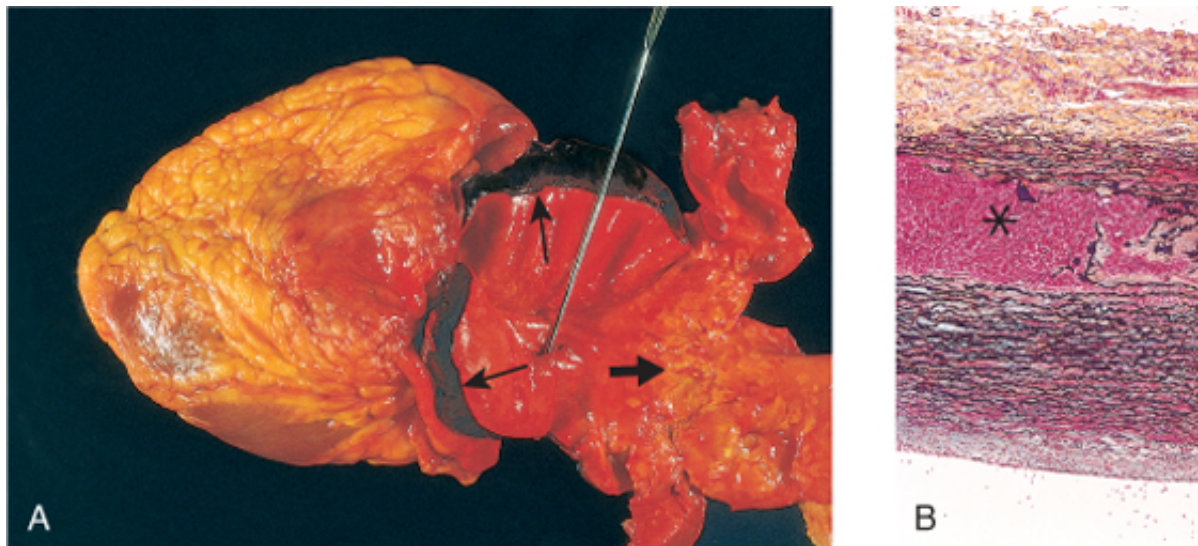
*T. pallidum* has a predilection to involve small blood vessels, the vasa vasorum, in the vessel wall. In these vessels develop so-called **obliterative endarteritis**. The affected vessels show luminal obliteration, scarring of the vessel wall, and a dense surrounding rim of lymphocytes that may extend into the media (**syphilitic aortitis**). The spirochetes are difficult to demonstrate.

The narrowing of the lumina of the vasa vasorum causes ischemic injury of the aorta. Loss of the medial elastic fibers and muscle cells, followed by inflammation and scarring of the media, the aorta loses its elastic recoil and may become dilated, producing an aneurysm. Fibrous scars may lead to wrinkling of intervening segments of aortic intima, grossly resembling "tree bark." Syphilitic involvement of the aorta favors the development of superimposed aortic root aneurysm, which can envelop and occlude the coronary ostia.

With weakening of the aortic root, the valvular annulus becomes dilated, resulting in aortic regurgitation and massive volume overload hypertrophy of the left ventricle. The greatly enlarged heart is called "cor bovinum" (cow's heart).

Thoracic aortic aneurysms (regardless of etiology) cause signs and symptoms referable to (1) encroachment on the lungs and airways, (2) respiratory difficulties caused by encroachment on the lungs and airways, (3) difficulty in swallowing the esophagus, (4) persistent cough from irritation of the recurrent laryngeal nerves, (5) pain caused by stretching of the chest wall, (6) cardiac disease due to valvular insufficiency or narrowing of the coronary ostia, and (7) syphilitic aneurysms die of heart failure induced by aortic valvular incompetence.

### Aortic Dissection



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Figure 10-19 Aortic dissection. **A**, Gross photograph of an opened aorta with proximal dissection originating from the intima (probe), allowing blood to enter the media and create an intramural hematoma (narrow arrows). Note that the intimal atherosclerotic plaque and that propagation of the intramural hematoma is arrested at a site more distally where at the view of the dissection demonstrating an aortic intramural hematoma (asterisk). Aortic elastic layers are black and blue stain.

Aortic dissection is a catastrophic event whereby blood solavs apart the laminar planes of the me



the aortic wall (see [Figs. 10-17](#) and [10-19](#)); this channel often ruptures through the adventitia and either massive hemorrhage or cardiac tamponade (hemorrhage into the pericardial sac). In contrast to aortic aneurysms, aortic dissection may or may not be associated with aortic dilation. Consequently, the prognosis is often discouraged.

Aortic dissection occurs principally in two epidemiologic groups: (1) men aged 40 to 60 years, with hypertension (90% of cases of dissection), and (2) younger patients with systemic or localized abnormalities of connective tissue (e.g., Marfan syndrome; [Chapter 7](#)). Dissections can also be iatrogenic (e.g., complicating arterial cannulation or cardiopulmonary bypass). Rarely, for unknown reasons, dissection of the aorta or other branch occurs during or after pregnancy. Dissection is unusual in the presence of substantial atherosclerosis or syphilis, presumably because the medial fibrosis inhibits propagation of the dissecting hematoma.

### *Pathogenesis*

Hypertension is *the* major risk factor for aortic dissection. Aortas in hypertensive patients show medial degeneration associated with ECM degenerative changes and variable loss of medial SMCs, suggesting that pressure and/or ischemic injury (due to diminished flow through the vasa vasorum) is somehow contributory. Nevertheless, the mechanisms by which hypertension causes aortic medial damage remain ill-defined. Moreover, recognizable medial damage does not guarantee dissection, nor a guarantee that dissection is imminent. Occasionally, dissections occur in the setting of minimal medial degeneration, and conversely marked degenerative changes are frequently seen at autopsies of patients who die of aortic dissection.

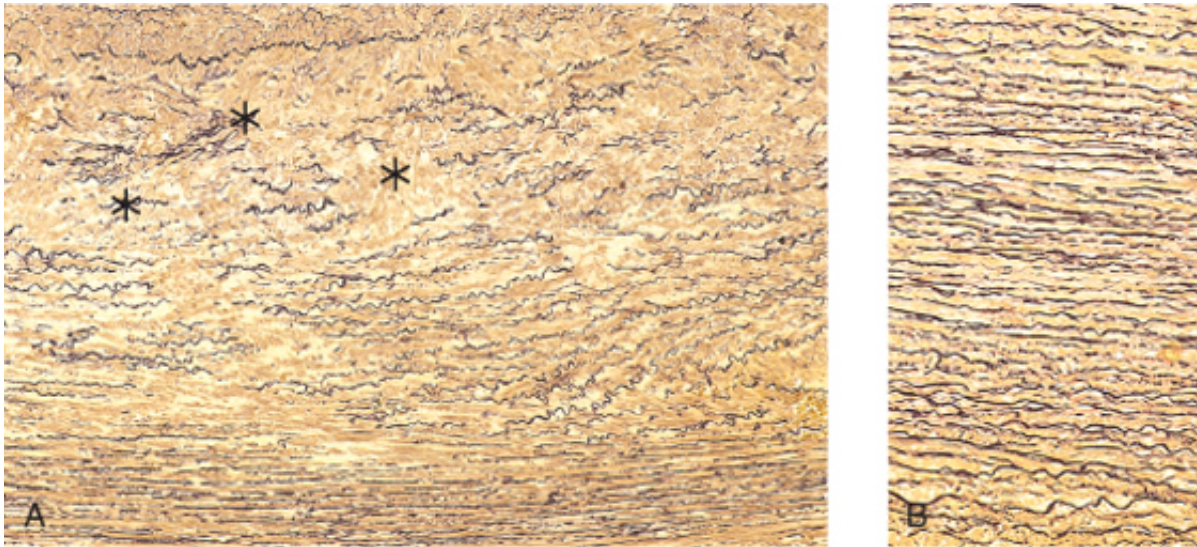
A considerably smaller number of dissections is related to inherited or acquired connective tissue disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome, vitamin C deficiency, copper metabolic defects). Marfan syndrome is probably the most common; it is an autosomal dominant disease of fibrillin, an ECM scaffolding protein involved in synthesis. Patients have skeletal abnormalities (elongated axial bones) and ocular findings (lens dislocation). Cardiovascular manifestations ([Chapter 7](#)).

Regardless of the underlying etiology that causes medial weakness, the trigger for the intimal tear is not known in most cases. Nevertheless, once the tear has occurred, blood flow under systemic pressure fosters progression of the medial hematoma. Accordingly, aggressive pressure-reducing therapy is indicated to prevent further dissection. In some cases, disruption of penetrating vessels of the vasa vasorum can give rise to a secondary intimal tear.

### **Morphology**

In the vast majority of spontaneous dissections, the intimal tear marking the point of origin is found in the ascending aorta, usually within 10 cm of the aortic valve (see [Fig. 10-17](#)). The tear is usually transverse or oblique and 1 to 5 cm in length, with sharp, jagged edges. The dissection extends along the aorta retrograde toward the heart as well as distally, sometimes all the way to the femoral arteries. The dissecting hematoma spreads characteristically along the lamellae, usually approximately between the middle and outer thirds (see [Fig. 10-19B](#)). It often ruptures through the adventitia, causing massive hemorrhage. In some (lucky) instances, the dissection extends into the lumen of the aorta, producing a second distal intimal tear and a new vascular channel within the aortic wall (and resulting in a "double-barreled aorta" with a false channel). This is often associated with massive hemorrhage. In the course of time, false channels may become endothelialized and may persist as chronic dissections.

In most cases, no specific underlying causal pathology can be identified in the aorta. The most common pre-existing histologically detectable lesion is cystic medial degeneration (CMD). CMD is characterized by elastic tissue fragmentation and separation of the elastic and SMC elements of the media, and replacement by the amorphous proteoglycan-rich ECM. Ultimately, there may be large spaces (see [Fig. 10-20](#)). Inflammation is characteristically absent. CMD of the aorta frequently occurs in Marfan syndrome, but patients with dissection caused by hypertension have variable nonspecific changes in aortic wall histology ranging from mild fragmentation of elastic tissue (most commonly) to



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Figure 10-20 Cystic medial degeneration. Elastin is stained *black*. **A**, Cross-section of aortic media from a patient with cystic medial degeneration, showing fragmentation and formation of areas devoid of elastin that resemble cystic spaces (*asterisks*). **B**, Normal media for comparison, showing a regular pattern of elastic tissue.

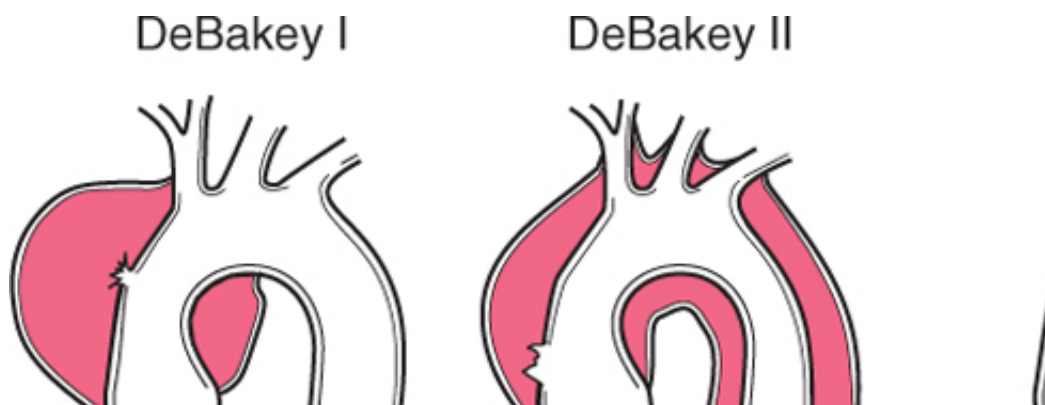
#### Clinical Course

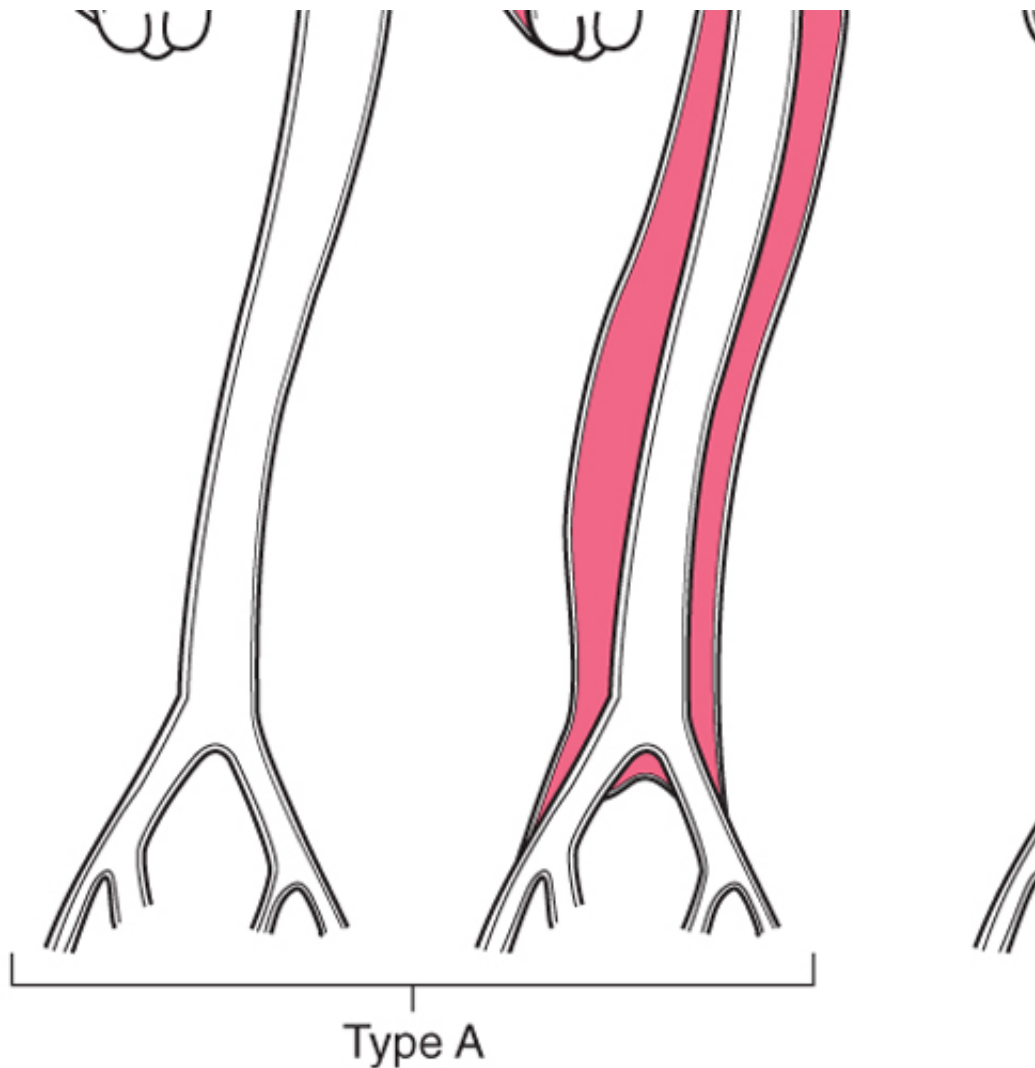
The risk and nature of serious complications of dissection depend strongly on the level of the aorta involved. Complications occur with dissections that involve the aorta from the aortic valve to the arch. Thus, dissections are divided into two types (Fig. 10-21):

The more common (and dangerous) *proximal* lesions (called *type A dissections*), involving the ascending and descending aorta (types I and II of the DeBakey classification). *Distal* lesions usually beginning distal to the subclavian artery (called *type B dissections* or DeBakey type

The classic clinical symptoms of aortic dissection are the *sudden onset of excruciating pain*, usually radiating to the back between the scapulae, and moving downward as the dissection progresses; myocardial infarction.

The most common cause of death is rupture of the dissection outward into any of the three body cavities (pleural, pericardial, or peritoneal). Retrograde dissection into the aortic root can cause disruption of the aortic valvular apparatus. Other manifestations include *cardiac tamponade*, *aortic insufficiency*, and *myocardial infarction* or extension of the dissection into the coronary, renal, mesenteric, or iliac arteries, causing critical vascular ischemia. Arteries may cause transverse myelitis.





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 Figure 10-21 Classification of dissections. Type A (proximal) involves the ascending aorta, either in isolation (DeBakey I) or involving the descending aorta (DeBakey II). Type B (distal, or DeBakey III) dissections arise after the take off of the great vessels. The serious dissections, which therefore mandate surgical intervention.

Previously, aortic dissection was typically fatal, but the prognosis has markedly improved. Rapid antihypertensive therapy, coupled with surgical procedures involving resection of the aorta permits



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## VASCULITIS

*Vasculitis*, or inflammation of vessel walls, occurs in diverse clinical settings. Depending on the vessel system (e.g., heart vs. small bowel), the manifestations can be protean. Besides the findings referred to above, clinical manifestations common to these entities typically include constitutional signs and symptoms such as fever, weight loss, and malaise.

Vessels of any type in virtually any organ can be affected, and most vasculitides can affect all sizes of vessels (e.g., arterioles, venules, and arteries). Nevertheless, several of the vasculitides tend to affect only vessels of particular caliber (e.g., giant-cell arteritis that primarily affects the aorta and medium-sized arteries, while others principally affect only small vessels). Several forms of vasculitis are recognized, and classification schemes attempt (with variable success) to categorize them on the basis of immune complexes, presence of specific autoantibodies, granuloma formation, organ tropism, and clinical features (Table 10-4). As we will see, there is considerable clinical and pathologic overlap among many of these entities.

The two most common pathogenic mechanisms of vasculitis are immune-mediated inflammation and infection. Predictably, *infections can also indirectly induce a noninfectious vasculitis*, either by forming immune complexes or triggering cross-reactivity. In any given patient, it is critical to distinguish between infectious and noninfectious vasculitis because immunosuppressive therapy is appropriate for immune-mediated vasculitis but could be harmful in infectious vasculitides. Physical and chemical injury, such as from irradiation, mechanical trauma, and toxins, can also cause vasculitis.

### Noninfectious Vasculitis

The main immunologic mechanisms that initiate noninfectious vasculitis are (1) immune complex deposition, (2) antineutrophil cytoplasmic antibodies (ANCA), and (3) anti-endothelial cell antibodies.

#### *Immune Complex-Associated Vasculitis*

**Table 10-4. Classification and Characteristics of Selected Immune-Mediated Vasculitides**

Vasculitis type*	Examples	Description
<i>Large-Vessel Vasculitis (Aorta and Large Branches to Extremities, Head, and Neck)</i>	<b>Giant-cell (temporal) arteritis</b>	Granulomatous inflammation; also frequently involves the aorta in patients older than age 50 and is associated with elevated erythrocyte sedimentation rate.
	<b>Takayasu arteritis</b>	Granulomatous inflammation usually occurring in patients younger than age 50, primarily involving the aorta and its major branches.
<i>Medium-Vessel Vasculitis (Main Visceral Arteries and Their Branches)</i>	<b>Polyarteritis nodosa</b>	Necrotizing inflammation typically involving renal and visceral arteries.
	<b>Kawasaki disease</b>	Arteritis with mucocutaneous lymph node syndrome; coronary arteries can be involved with aneurysm formation.
<i>Small-Vessel Vasculitis (Arterioles, Venules, Capillaries, and Occasionally Small Arteries)</i>	<b>Wegener granulomatosis</b>	Granulomatous inflammation involving the respiratory tract and kidneys, affecting small vessels, including glomerulonephritis.
	<b>Churg-Strauss syndrome</b>	Eosinophil-rich and granulomatous inflammation in necrotizing vasculitis affecting small vessels. Associated with eosinophilia. Associated with p-ANCA.
	<b>Microscopic polyangiitis</b>	Necrotizing small-vessel vasculitis with few or no immune complexes; small and medium-sized arteries can occur. Necrotizing capillaritis are common. Associated with p-ANCA.

\*Note that some small- and large-vessel vasculitides may involve medium-sized arteries, but large- and medium-sized vessel vasculitides typically do not involve small vessels.

Modified from Jennette JC, et al. Nomenclature of systemic vasculitides: The proposal of an international consensus conference. *Am J Med* 1990;88:1-2. ANCA, antineutrophil cytoplasmic antibodies; cytoplasmic localization; p-ANCA, antineutrophil cytoplasmic antibodies, perinuclear localization.

The lesions resemble those found in experimental immune complex-mediated conditions (e.g., see below). Complement is typically detected in vasculitic lesions, although the nature of the antigens responsible cannot be determined. Circulating immune (antigen-antibody) complexes may also be seen—for example, in systemic lupus erythematosus (SLE)-associated vasculitis (Chapter 5). Several examples follow:

Immune complex deposition underlies the vasculitis associated with drug hypersensitivity. Drugs can bind to serum proteins; other agents, like streptokinase<sup>®</sup>, are themselves foreign proteins. Antibodies against the drug-modified self proteins or foreign molecules lead to the formation of immune complexes across the spectrum of vasculitides, frequently involving the skin (see below), and can be recurrent and even fatal. It is important to identify such disorders as drug hypersensitivities, since discontinuation is curative. In vasculitis associated *secondarily* with viral infections, antibody to viral proteins is found in the serum and in the vascular lesions; for example, as many as 30% of patients with polyarteritis nodosa underlying hepatitis B infection with vasculitis attributable to complexes of hepatitis B surface antigen (HBsAg).

In most cases, it is not clear whether the antigen-antibody complexes form elsewhere and then migrate to the vessel wall or if they form in situ from the seeding of antigen in a vessel wall, with subsequent antibody deposition. In cases of presumed immune complex vasculitis, there is a distressing scarcity of antigen-antibody complexes; they have been largely degraded at the time that the tissue diagnosis is made, or only small amounts of such "pauci-immune" vasculitides.

#### *Antineutrophil Cytoplasmic Antibodies*

Many patients with vasculitis have circulating antibodies that react with neutrophil cytoplasmic antigens, a heterogeneous group of autoantibodies directed against constituents (mainly enzymes) of neutrophil granules, lysosomes, and endothelial cells. Two general types of ANCA are recognized based on immunofluorescent localization:

Cytoplasmic localization (c-ANCA), wherein the most common target antigen is proteinase 3 (PR3)  
Perinuclear localization (p-ANCA), wherein most of the autoantibodies are specific for myeloperoxidase (MPO)

Either ANCA specificity can occur in ANCA-associated vasculitides, but *c-ANCA is typical of Wegener's granulomatosis and microscopic polyangiitis, and p-ANCA is typical of Churg-Strauss syndrome* (see below).

ANCAs serve as useful quantitative diagnostic markers for the ANCA-associated vasculitides, and as indicators of disease activity. Perhaps more significantly, the close association between ANCA titers and disease activity suggests a pathogenic role. Although the precise mechanisms are unknown, ANCAs can directly activate neutrophils, leading to an inflammatory state that continually recruits and stimulates neutrophils to release reactive oxygen species and proteolytic enzymes. Moreover, although the antigenic targets of ANCAs are primarily intracellular and therefore might not be accessible to circulating antibodies, newer evidence suggests that ANCA antigens (in particular PR3) may be exposed on the plasma membrane or translocated to the cell surface in activated neutrophils.

A plausible mechanism for ANCA vasculitis is:

Neutrophil release of PR3 and MPO (e.g., in the setting of infections) incites ANCA formation. Infection or other disorder (e.g., infection, endotoxin exposure, etc.) elicits inflammatory cytokines, such as TNF- $\alpha$ , which activate neutrophils to release PR3 and MPO on neutrophils and other cell types. ANCAs react with these cytokine-primed antigens (e.g., on endothelium) or induce activation (e.g., in neutrophils). ANCA-activated neutrophils degranulate, releasing reactive oxygen species, engendering EC toxicity and other direct tissue injury.

Interestingly, ANCAs directed against constituents other than PR3 and MPO are also found in disorders that do not involve vasculitis (e.g., inflammatory bowel disease, primary sclerosing cholangitis, and Sjögren's syndrome).

#### *Anti-Endothelial Cell Antibodies*

Antibodies to ECs may predispose to certain vasculitides, for example Kawasaki disease (see below).

We will now briefly present several of the best characterized and generally recognized vasculitides.



we will now briefly present several of the best-characterized and generally recognized vasculitides overlap among the different entities. Moreover, it should be kept in mind that any given patient may have findings that allows the clinician to settle on a specific diagnosis.

### **Giant-Cell (Temporal) Arteritis**

Giant-cell (temporal) arteritis is the most common of the vasculitides. It is a chronic, typically granulomatous inflammation of medium-sized arteries; it principally affects the arteries in the head-especially the temporal arteries-but also as well as the aorta (*giant-cell aortitis*). Ophthalmic artery involvement can lead to sudden and permanent vision loss.

#### **Pathogenesis**

The cause of giant-cell arteritis remains elusive, although the bulk of the evidence supports a T cell-mediated process. The antigen is unknown, possibly vessel wall, antigen. An immune origin is supported by the characteristic granulomatous inflammation, the presence of helper T cells, a correlation with certain major histocompatibility complex (MHC) class II haplotype, and response to corticosteroids. The extraordinary predilection for a single vascular site (temporal artery) remains unexplained.

#### **Morphology**

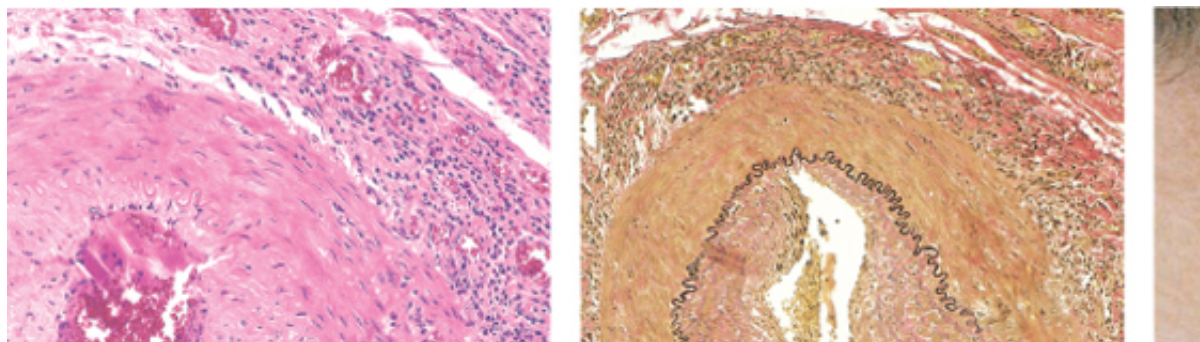
Involved arterial segments in giant-cell arteritis develop **nodular intimal thickening** and occasional thrombosis. Classical lesions show **granulomatous inflammation** of the intima centered on the internal elastic lamina; there is a lymphocyte (CD4+ macrophage) infiltrate, with multinucleated giant cells, and **fragmentation of the internal elastic lamina** (10-22). Occasionally, granulomas and giant cells are rare or absent, and lesions resemble polyarteritis nodosa with a mixed infiltrate composed predominantly of lymphocytes and macrophages, with occasional neutrophils and eosinophils. Inflammatory lesions are not continuous along the vessel; intervening segments of relatively normal artery may separate areas of inflammation. The healed stage of the disease is characterized by collagenous thickening of the vessel wall; organization of a luminal thrombus can take the form of a fibrous cord. End-stage scarring may be difficult to distinguish from age-associated atherosclerosis.

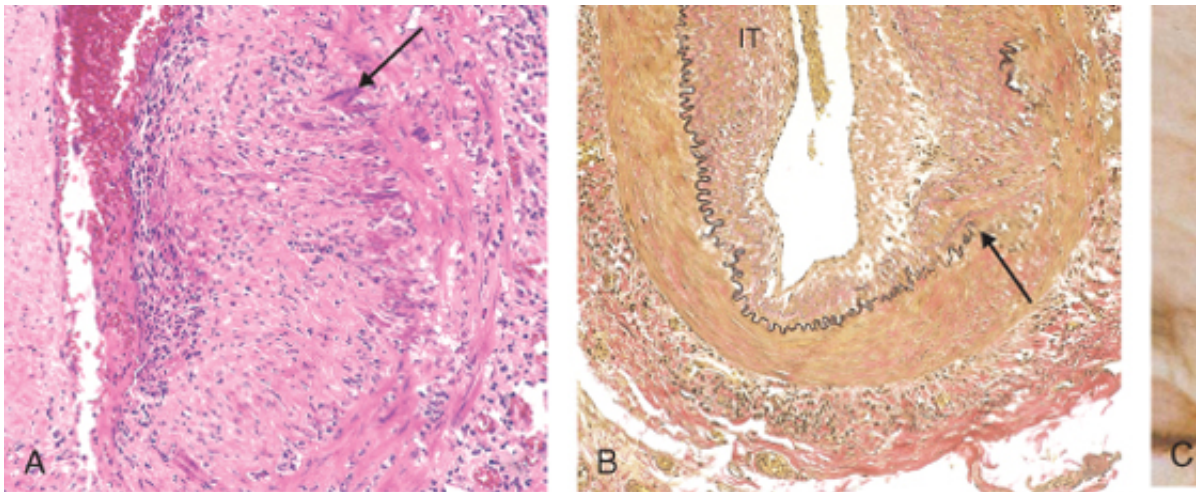
#### **Clinical Features**

Temporal arteritis occurs only rarely in persons younger than 50 years of age. Symptoms may be nonspecific, such as fatigue, weight loss-or may involve facial pain or headache, most intense along the course of the artery and often relieved by massage or heat. Ocular symptoms (associated with involvement of the ophthalmic artery) abruptly develop and range from diplopia to complete vision loss. Diagnosis depends on biopsy and histologic confirmation. The disease is extremely segmental, adequate biopsy requires at least a 2- to 3-cm length of artery; even a negative biopsy does not exclude the diagnosis. Treatment with corticosteroids is generally effective.

### **Takayasu Arteritis**

This is a granulomatous vasculitis of medium and larger arteries characterized principally by occlusion of the aorta and its major branches. It is characterized by the absence of the pulses in the upper extremities (hence its other name, "pulseless disease"). Takayasu arteritis involves the aorta-particularly the aortic arch and great vessels-with severe luminal narrowing. It occurs most frequently in women younger than 40 years of age; although traditionally associated with the Far East, it has a worldwide distribution. The cause and pathogenesis are unknown, although immune mechanisms are suspected.





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 Figure 10-22 Temporal (giant-cell) arteritis. **A**, H+E-stained section of temporal artery showing giant cells at the de  
 Elastic tissue stain demonstrating focal destruction of internal elastic membrane (*arrow*) and intimal thickening (*IT*)  
**C**, Temporal artery of a patient with temporal arteritis showing a thickened, nodular, and tender segment of a ve  
 Salvarani C, et al.: Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 347:261-271, 2002. Copyright ©  
 reserved.)

### Morphology

Takayasu arteritis classically involves the **aortic arch** but in a third of cases also a  
 aorta and its branches; pulmonary arteries are involved in 50% of patients. Gross c  
 hyperplasia and irregular thickening of the vessel wall; when the aortic arch is invo  
 great vessels can be markedly narrowed or even obliterated (Fig. 10-23A and B). §  
 the weakness of the peripheral pulses; coronary and renal arteries may be similarly  
 the changes range from adventitial mononuclear infiltrates with perivascular cuffing  
 intense mononuclear inflammation in the media, to granulomatous inflammation, re  
 patchy medial necrosis. The histology (Fig. 10-23C) may be indistinguishable from  
**distinctions between active giant-cell lesions of the aorta are based largely o**  
**most aortic giant-cell lesions in young patients (age 40 years and younger) a**  
**Takayasu aortitis.** As the disease progresses, collagenous scarring, with admixed  
 infiltrates, occurs in all three layers of the vessel wall. Prominent intimal involveme  
 narrowing and obliteration. Occasionally, aortic root involvement causes dilation ar  
 insufficiency.

### Clinical Features

Initial symptoms are usually nonspecific, including fatigue, weight loss, and fever. With progressio  
 dominate the clinical picture. These include *reduced blood pressure and weaker pulses in the uppe*  
*extremities*, with coldness or numbness of the fingers; ocular disturbances, including visual defect  
 blindness; and neurologic deficits. Involvement of the more distal aorta may lead to claudication o  
 may cause pulmonary hypertension. Narrowing of the coronary ostia may lead to myocardial infar  
 arteries leads to systemic hypertension in roughly half of patients. The course of the disease is va  
 progression, but in others a quiescent stage is reached in 1 to 2 years, permitting long-term surviv  
 neurologic deficits.

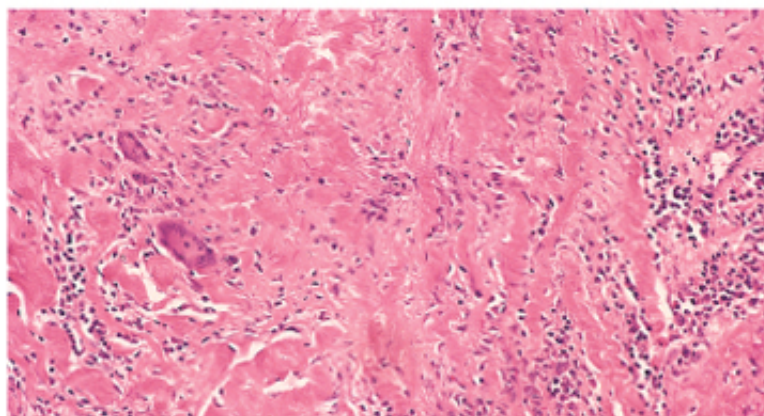
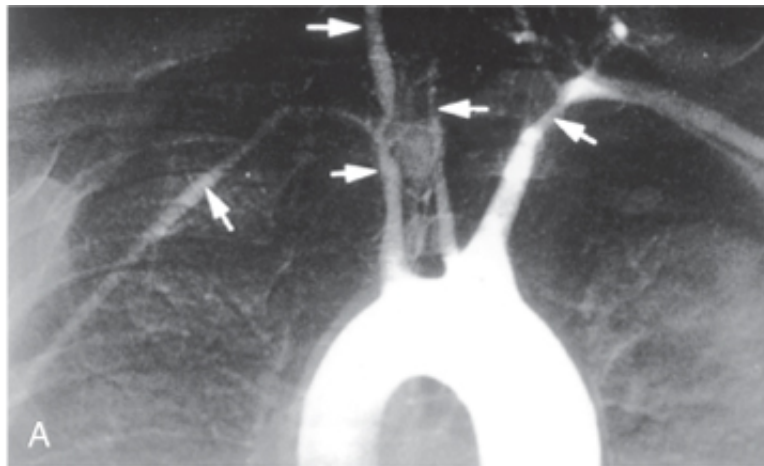
### Polyarteritis Nodosa

*Polyarteritis nodosa* (PAN) is a systemic vasculitis of small or medium-sized muscular arteries (bu  
 typically involving renal and visceral vessels but sparing the pulmonary circulation.

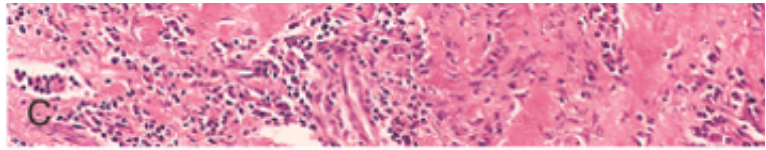
### Morphology

Classic PAN is characterized by segmental transmural necrotizing inflammation of **arteries**. Vessels of the kidneys, heart, liver, and GI tract are involved in descending order. Lesions usually involve only **part of the vessel circumference**, with a predilection for the **superior** aspect. The inflammatory process weakens the arterial wall and can lead to aneurysms or even rupture. Ischemia with ulcerations, infarcts, ischemic atrophy, or hemorrhages in the distribution of the affected vessel may be the first sign of disease.

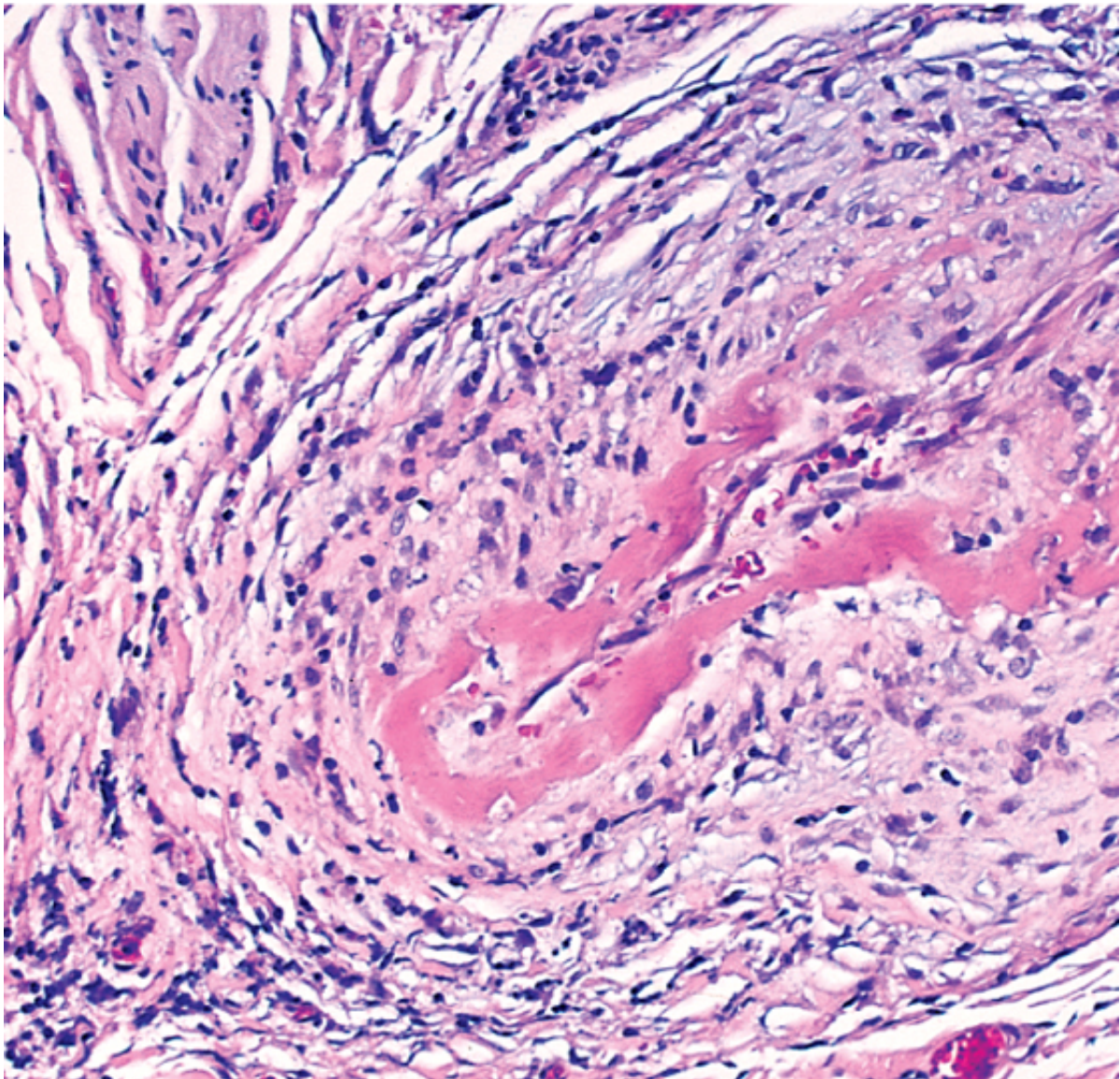
During the acute phase there is **transmural inflammation** of the arterial wall with infiltration by neutrophils, eosinophils, and mononuclear cells, frequently accompanied by **fibrin** deposition. Luminal thrombosis can occur. Later, the acute inflammatory infiltrate is replaced by a chronic (nodular) thickening of the vessel wall that can extend into the adventitia. Characteristic of PAN is that different stages of activity (from early to late) may coexist in different vessels or even within the same vessel.







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 Figure 10-23 Takayasu arteritis. **A**, Aortic arch angiogram showing narrowing of the brachiocephalic, carotid, and s of two cross-sections of the right carotid artery from the patient shown in **A**, demonstrating marked intimal thickening of active Takayasu aortitis, illustrating destruction and fibrosis of the arterial media and an infiltrate of mononuclear cells.



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 Figure 10-24 Polyarteritis nodosa. There is segmental fibrinoid necrosis and thrombotic occlusion of the lumen of the upper right (arrow) is uninvolved. (Courtesy of Dr. Sidney Murphree, Department of Pathology, University of Texas.)

### *Clinical Course*

PAN is a disease primarily of young adults, but it can occur at all ages. The course can vary from

with long symptom-free intervals. Because the vascular involvement is widely scattered, the clinical picture is often nonspecific. The most common manifestations are malaise, fever, and weight loss; hypertension, usually developing in the setting of renal (arterial) involvement; melena (bloody stool) caused by vascular GI lesions; diffuse muscular aches and pains; and peripheral neuropathy. Renal (arterial) involvement is common and a major cause of death, although glomerulonephritis is absent. Biopsy is often necessary to confirm the diagnosis. There is no association between PAN and hepatitis B antigenemia, and HBsAg-HBsAb immune complexes can be detected in some patients. The disease is fatal in most cases; therapy with corticosteroids and cyclophosphamide<sup>Rx</sup> results in

### **Kawasaki Disease**

Kawasaki disease is an acute febrile, usually self-limited illness of infancy and childhood (80% of cases are associated with an arteritis affecting large to medium-sized, and even small vessels). Its clinical signs include fever, rash, conjunctivitis, coronary arteritis; coronary arteritis can result in aneurysms that rupture or thrombose, causing acute myocardial infarction. The disease is the leading cause of acquired heart disease in children. Originally described in Japan, it is now found in the United States and other countries.

#### **Pathogenesis**

The etiology is uncertain, but the vasculitis is thought to result from a delayed-type hypersensitivity reaction to an uncharacterized vascular antigen. This leads to cytokine production, with B-cell activation and the release of antibodies. The autoantibodies precipitate the acute vasculitis. It is speculated that in genetically susceptible individuals, agents (most likely viral) can trigger the disease.

#### **Morphology**

The vasculitis of Kawasaki disease is PAN-like, with pronounced inflammation affecting the vessel wall; nevertheless, the fibrinoid necrosis is usually less prominent than in PAN. Although the acute vasculitis subsides spontaneously or in response to treatment, it can result in thrombosis and myocardial infarction, can supervene. As with other causes of arterial disease, it can have obstructive intimal thickening. Pathologic changes outside the cardiovascular system are usually insignificant.

#### **Clinical Course**

Kawasaki disease is also called *mucocutaneous lymph node syndrome*, so named because it presents with fever, rash, and edema of the hands and feet, erythema of the palms and soles, a desquamative rash on the fingers and toes. Approximately 20% of untreated patients develop cardiovascular sequelae, ranging from asymptomatic coronary artery ectasia and aneurysm formation, to giant coronary artery aneurysms (7-8 mm) with rupture and sudden death. With intravenous immunoglobulin therapy, the rate of coronary artery disease is reduced.

### **Microscopic Polyangiitis**

This is a necrotizing vasculitis that generally affects capillaries as well as arterioles and venules of small and medium size; rarely, larger arteries may be involved. It is also called hypersensitivity vasculitis or leukocytoclastic vasculitis. *Microscopic polyangiitis tends to be of the same age in any given patient.* The skin, mucous membranes, kidneys, and muscle can all be involved; *in contrast to PAN, necrotizing glomerulonephritis (90% of cases) is particularly common.* Disseminated vascular lesions of hypersensitivity angiitis can also occur as in Henoch-Schönlein purpura, essential mixed cryoglobulinemia, and vasculitis associated with connective tissue diseases.

#### **Pathogenesis**

In many cases, an antibody response to antigens such as drugs (e.g., penicillin), microorganisms, or tumor proteins is the presumed cause. This can result in immune complex deposition, which is ultimately causal; in this regard it is noteworthy that p-ANCA are present in many patients and activation of neutrophils within a particular vascular bed are probably responsible for the manifestation of the disease.

#### **Morphology**

Microscopic polyangiitis is characterized by segmental fibrinoid necrosis of the medium-sized vessels. In contrast to PAN, necrotizing lesions: granulomatous inflammation is absent. These lesions morphologically resemble those of PAN.



neutrophilic leukocytes; granulomatous inflammation is absent. These lesions most often typically spare medium-sized and larger arteries; consequently, PAN-like macroscopic changes are uncommon. In some areas (typically post-capillary venules), only infiltrating and fragmentation of red blood cells are seen, giving rise to the term **leukocytoclastic vasculitis** (Fig. 10-25A). Although immunofluorescent complement components can be demonstrated in early skin lesions, **little or no immune reaction is seen in most lesions (so-called "pauci-immune" injury)**.

#### Clinical Course

Depending on the vascular bed involved, major clinical features include hemoptysis, hematuria, arthralgia, muscle pain or weakness; and palpable cutaneous purpura. With the exception of those who develop renal involvement, most patients respond to simple removal of the offending agent.

#### Wegener Granulomatosis

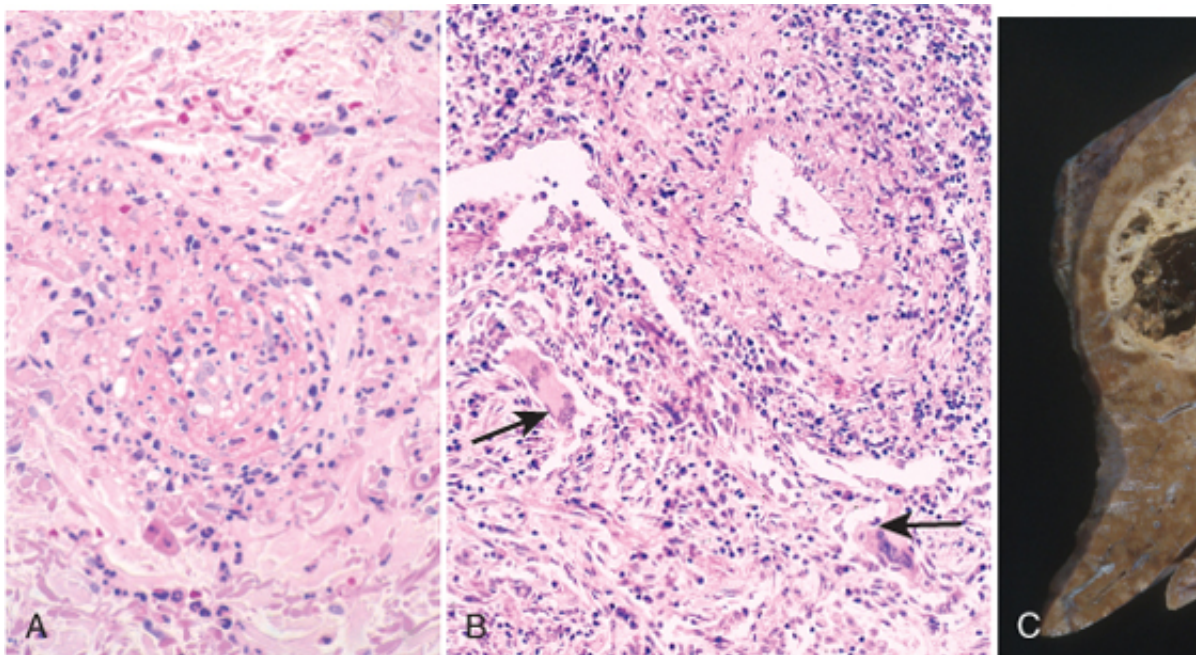
Wegener granulomatosis is a necrotizing vasculitis characterized by a triad of

*Acute necrotizing granulomas of the upper respiratory tract (ear, nose, sinuses, throat) or the lungs; both Necrotizing or granulomatous vasculitis affecting small to medium-sized vessels (e.g., arteries), most prominent in the lungs and upper airways but affecting other sites as well; and Renal involvement, necrotizing, often crescentic, glomerulonephritis.*

"Limited" forms of Wegener granulomatosis may be restricted to the respiratory tract. Conversely, severe forms may affect eyes, skin, and other organs, notably the heart; clinically, this resembles PAN except that there is no renal involvement.

#### Pathogenesis

Wegener granulomatosis probably represents some form of cell-mediated hypersensitivity response to an unknown environmental agent; such a pathogenesis is supported by the presence of granulomas and the response to immunosuppressive therapy. c-ANCA are present in up to 95% of cases; they are a useful marker of disease pathogenesis. Following immunosuppressive treatment, a rising c-ANCA titer suggests relapse, a negative test, or the titer falls significantly.



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Figure 10-25 Representative forms of ANCA-associated small-vessel vasculitis. **A**, Microscopic polyangiitis (leukocytoclastic vasculitis) with neutrophils in and around blood vessel walls. **B** and **C**, Wegener granulomatosis. **B**, Vasculitis of a small artery with epithelioid cells and giant cells (arrows). **C**, Gross photo from the lung of a patient with fatal Wegener granulomatosis.

epithelioid cells and giant cells (arrows). **C**, Gross photo from the lung of a patient with fatal Wegener granulomatosis with cavitating lesions. (**A**, Courtesy of Dr. Scott Granter, Brigham and Women's Hospital, Boston, Massachusetts. **C**, (Pathology, University of Texas Southwestern Medical School, Dallas, TX)

## Morphology

The **upper respiratory** tract lesions of Wegener granulomatosis range from **inflamed mucosal granulomas to ulcerative lesions of the nose, palate, or pharynx, rimmed with geographic patterns of central necrosis** and accompanying vasculitis (Fig. 10-25A). Granulomas are surrounded by a zone of fibroblastic proliferation with giant cells, suggesting the possibility of mycobacterial or fungal infections. Multiple granuloma radiographically visible nodules that can also cavitate; late-stage disease may be characterized by necrotizing granulomatous involvement of the parenchyma (Fig. 10-25C), and alveoli may ultimately undergo progressive fibrosis and organization.

The **renal lesions** (Chapter 14) range over a spectrum. At one end, there is mild glomerulonephritis; glomeruli show acute focal necrosis with thrombosis of isolated glomerular capillaries (segmental necrotizing glomerulonephritis). More advanced glomerular lesions are characterized by glomerular necrosis and parietal cell proliferation to form crescents (**crescentic glomerulonephritis**). Mild lesions may have only hematuria and proteinuria responsive to therapy, whereas the severe form can develop rapidly progressive renal failure.

## Clinical Features

Males are affected more often than are females, at an average age of about 40 years. Classical features include bilateral nodular and cavitary infiltrates (95%), chronic sinusitis (90%), mucosal ulcerations of the nose (90%), and renal disease (80%). Other features include rashes, muscle pains, articular involvement, mononeuropathy, and hearing loss. If untreated, the course of the disease is malignant; 80% of patients die within 1 year.

*Allergic granulomatosis and angiitis (Churg-Strauss syndrome)* is a related entity distinguished by the presence of *asthma*, *peripheral eosinophilia*, and *p-ANCA*s; p-ANCA is present in roughly half the patients. Lesions can resemble PAN and microscopic polyangiitis, but in the lung, heart, spleen, peripheral nerves, and skin, there are intravascular and extravascular granulomas, with striking infiltration of vessels and perivascular tissue. In Churg-Strauss syndrome, severe renal disease is infrequent; instead, coronary artery disease is a major cause of morbidity and mortality.

## Thromboangiitis Obliterans (Buerger Disease)

*Thromboangiitis obliterans (Buerger disease)* is a distinctive disease that often leads to vascular infarction. It is characterized by segmental, thrombosing acute and chronic inflammation of medium-sized and small arteries, principally in the extremities, with occasional secondary extension into extremity veins and nerves. Buerger disease is a condition that affects young smokers of cigarettes, usually beginning before age 35.

## Pathogenesis

The strong relationship to cigarette smoking is thought to involve direct toxicity to endothelium by an idiosyncratic immune response to the same agents. Most Buerger patients have hypersensitivity to cigarette smoke and their vessels show impaired endothelium-dependent vasodilation when challenged with acetylcholine. The disease is suggested by an increased prevalence in certain ethnic groups (Israeli, Indian subcontinent, Japanese) and by certain MHC haplotypes.

## Morphology

Thromboangiitis obliterans is characterized by a **sharply segmental acute and chronic inflammation of medium-sized and small arteries, predominantly of the extremities**. Microscopically, there is acute and chronic inflammation, accompanied by luminal thrombosis. Typically, the thrombus is composed of neutrophils surrounded by granulomatous inflammation. The thrombus may eventually organize and recanalize. The inflammatory process extends to the surrounding nerves and nerves (rare with other forms of vasculitis), and in time all three structures become involved.

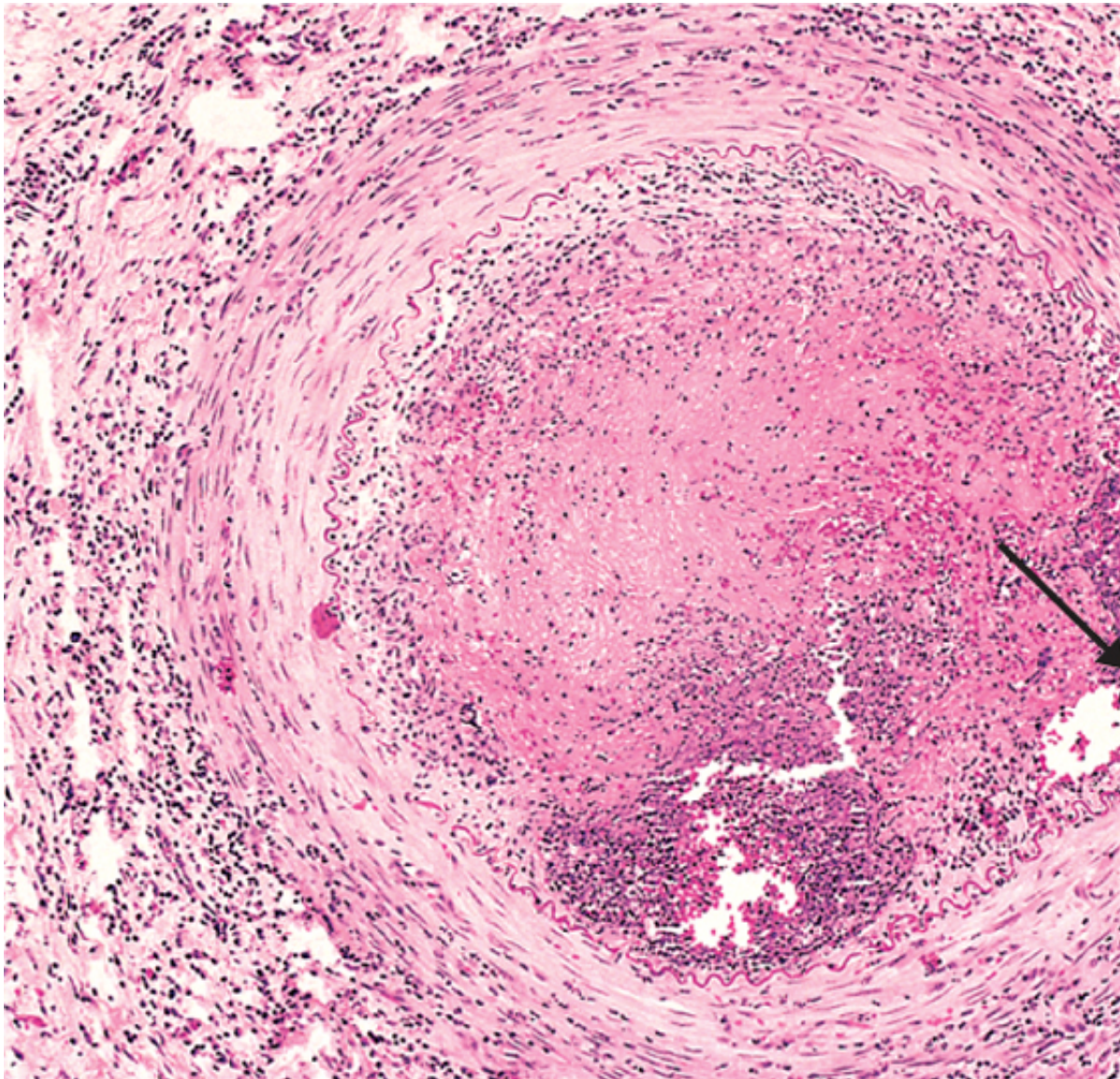


tissue.

### **Clinical Features**

The early manifestations are a superficial nodular phlebitis, cold sensitivity of the Raynaud type (sometimes of the foot induced by exercise (so-called *instep claudication*). In contrast to the vascular insufficiency in Buerger disease the insufficiency tends to be accompanied by severe pain, even at rest, related to the ischemia. Chronic ulcerations of the toes, feet, or fingers may appear, perhaps followed in time by frank gangrene. Smoking in the early stages of the disease often brings dramatic relief from further attacks.

### **Vasculitis Associated with Other Disorders**



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Figure 10-26 Thromboangiitis obliterans (Buerger disease). The lumen is occluded by a thrombus containing abundant leukocytes.

Vasculitis resembling hypersensitivity angiitis or classic PAN may sometimes be associated with systemic lupus erythematosus, rheumatoid arthritis, SLE, malignancy, or systemic illnesses such as mixed cryoglobulinemia, antiphospholipid syndrome.

Henoch-Schönlein purpura. *Rheumatoid vasculitis* occurs predominantly after long-standing, severe small and medium-sized arteries, leading to visceral infarction; it may also cause a clinically significant pathology may be therapeutically important. For example, distinguishing between *lupus vasculitis* and similar antiphospholipid antibody syndrome is clinically important, as aggressive anti-inflammatory and aggressive anticoagulant therapy is indicated in the latter.

### **Infectious Vasculitis**

Localized arteritis may be caused by the direct invasion of infectious agents, usually bacteria or fungi. *Mucor* species. Vascular invasion can be part of a more general tissue infection (e.g., bacterial pneumonia) or less commonly it may arise from hematogenous spread of bacteria during septicemia or embolization.

Vascular infections can weaken arterial walls and give rise to *mycotic aneurysms* (see earlier), or infarction. Thus, involvement of meningeal vessels in bacterial meningitis can cause thrombosis and a subarachnoid infection into the brain parenchyma.

### **SUMMARY Vasculitis**

Vasculitis is inflammation of the vessel wall; although there are frequently systemic symptoms (including fever, malaise, myalgias, and arthralgias), specific symptoms depend on the vessel type that is involved. Vasculitis can result from infections, but it more commonly results from immune-mediated processes such as immune complex deposition, ANCA, or anti-EC antibodies. Different types of vasculitis tend to specifically affect vessels of a particular caliber and location (summarized in Table 1).



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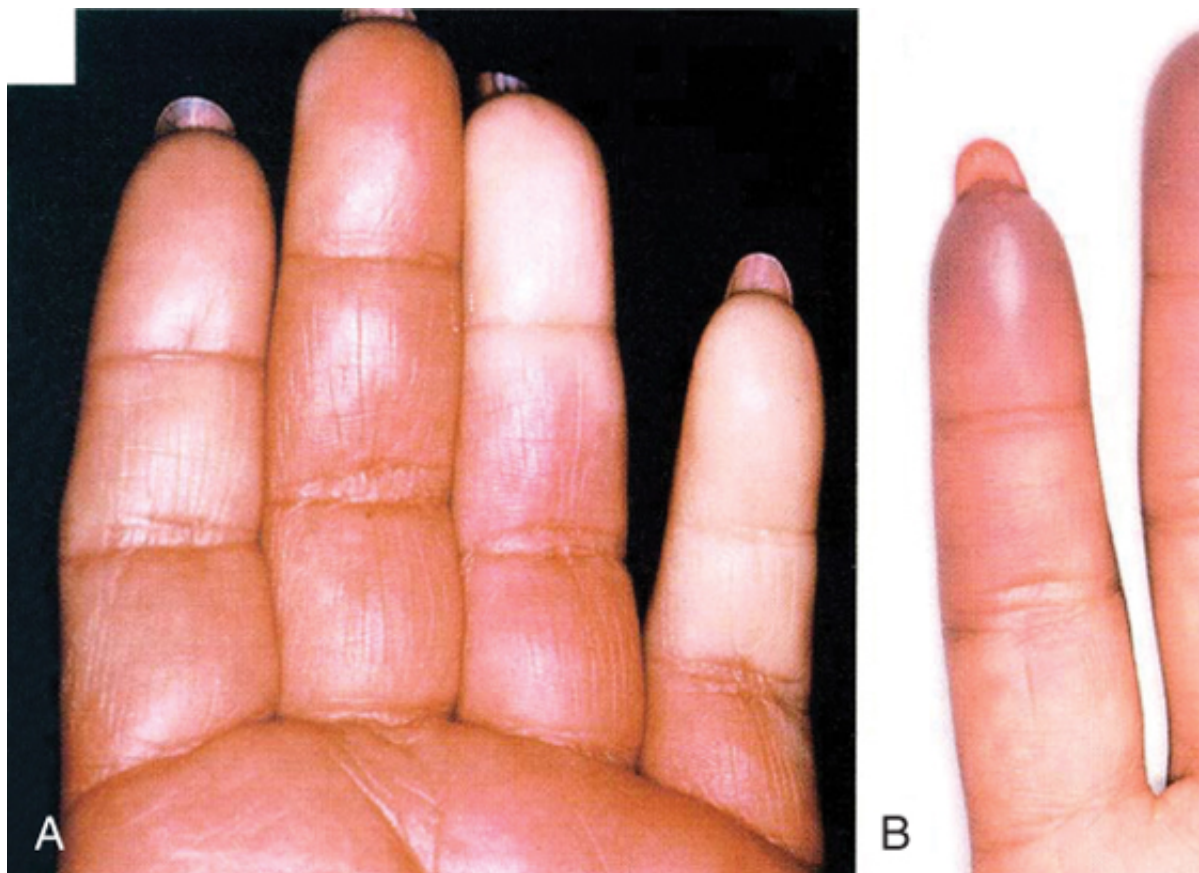




## RAYNAUD PHENOMENON

*Raynaud phenomenon* results from an exaggerated vasoconstriction of digital arteries and arterioles, causing paroxysmal pallor or cyanosis of the digits of the hands or feet; infrequently, the nose, earlobes, or lips. Characteristically, the involved digits show red, white, and blue color changes from most proximal to most distal: vasodilation, central vasoconstriction, and more distal cyanosis (Fig. 10-27). Raynaud phenomenon can be primary or secondary to a variety of conditions.

*Primary Raynaud phenomenon* (previously called Raynaud disease) reflects an exaggeration of the normal response to cold or emotion, with a prevalence in the general population of 3% to 5% and a predilection for young women. The arterial walls are absent except late in the course, when intimal thickening can appear. The course is usually benign, but long-standing, chronic cases can result in atrophy of the skin, subcutaneous tissue, and even ischemic gangrene are rare.



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Figure 10-27 Raynaud phenomenon. **A**, Sharply demarcated pallor of the distal fingers resulting from the closure of digital arteries. (From Salvarani C, et al.: Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002; 346: 1783-1790.)

In contrast, *secondary Raynaud phenomenon* refers to vascular insufficiency of the extremities in other entities including SLE, scleroderma, Buerger disease, or even atherosclerosis. Indeed, since the manifestation of such conditions, any patient with symptoms should be evaluated; 10% will eventually develop secondary Raynaud phenomenon.



## VEINS AND LYMPHATICS

Varicose veins and phlebothrombosis/thrombophlebitis together account for at least 90% of clinical disease associated with veins.

### **Varicose Veins**

Varicose veins are abnormally dilated, tortuous veins produced by prolonged increase in intraluminal pressure and loss of vessel wall support. The *superficial veins* of the upper and lower leg are typically involved (Fig. 10-28). When legs are dependent for long periods, venous pressures in these sites can be markedly elevated (up to 10 times normal) and can lead to venous stasis and pedal edema, even in essentially normal veins (*simple orthostatic edema*). Some 10% to 20% of adult males and 25% to 33% of adult females develop lower extremity varicose veins; obesity increases the risk, and the higher incidence in women is a reflection of the elevated venous pressure in lower legs caused by pregnancy. A *familial tendency* toward premature varicosities results from imperfect venous wall development.





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Figure 10-28 Varicose veins of the leg (arrow). (Courtesy of Dr. Magruder C. Donaldson, Brigham and Women's Hospital, Boston, Massachusetts.)

### Morphology

Varicose veins show wall thinning at the points of maximal dilation with smooth muscle hypertrophy and intimal fibrosis in adjacent segments; elastic tissue degeneration and spotty medial calcifications (phlebosclerosis) also occur. Focal intraluminal thrombosis (due to stasis) and venous valve deformities (rolling and shortening) are common.

### Clinical Course

Varicose dilation renders the venous valves incompetent and leads to stasis, congestion, edema, pain, and thrombosis. The most disabling sequelae include persistent edema in the extremity and secondary ischemic skin changes including stasis dermatitis and ulcerations; poor wound healing and superimposed infections can become chronic *varicose ulcers*. *Notably, embolism from these superficial veins is very rare. This is in sharp contrast to the relatively frequent thromboembolism that arises from thrombosed deep veins* (see below and Chapter 4).

Varicosities also occur in two other sites that deserve mention:

**Esophageal varices.** Liver cirrhosis (less frequently, portal vein obstruction or hepatic vein thrombosis) causes portal vein hypertension (Chapter 16). Portal hypertension leads to the opening of porto-systemic shunts, increasing blood flow into veins at the gastroesophageal junction (forming *esophageal varices*), the rectum (forming *hemorrhoids*), and periumbilical veins of the abdominal wall (forming a *caput medusa*). Esophageal varices are the most important, since their rupture can lead to massive (even fatal) upper GI hemorrhage. *Hemorrhoids* can also result from primary varicose dilation of the venous plexus at the anorectal junction (e.g., through prolonged pelvic vascular congestion due to pregnancy or straining to defecate). Hemorrhoids are uncomfortable and may be a source of bleeding; they can also thrombose and are prone to painful ulceration.

### Thrombophlebitis and Phlebothrombosis

*The deep leg veins account for more than 90% of cases of thrombophlebitis and phlebothrombosis*; the two terms are largely interchangeable designations for venous thrombosis and inflammation. The periprostatic venous plexus in males and the pelvic venous plexus in females are additional sites, as are the large veins in the skull and the dural sinuses (especially in the setting of infection or inflammation). Peritoneal infections (e.g., peritonitis, appendicitis, salpingitis, and pelvic abscesses) can lead to portal vein thrombosis. For deep venous thrombosis (DVT) of legs, *congestive heart failure, neoplasia* (see below), *pregnancy*,



*obesity, the postoperative state, and prolonged bed rest or immobilization are the most important clinical predispositions.* Genetic hypercoagulability syndromes (Chapter 4) can also be associated with venous thrombosis.

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In patients with cancer, particularly adenocarcinomas, hypercoagulability occurs as a paraneoplastic syndrome related to tumor elaboration of procoagulant factors (Chapter 6). In this setting, venous thromboses classically appear in one site, disappear, and then reoccur in other veins, so-called *migratory thrombophlebitis (Trousseau sign)*.

Thrombi in the legs tend to produce few, if any, reliable signs or symptoms. Indeed, local manifestations, including distal edema, cyanosis, superficial vein dilation, heat, tenderness, redness, swelling, and pain may be entirely absent, especially in bedridden patients. In some cases, pain can be elicited by pressure over affected veins, squeezing the calf muscles, or forced dorsiflexion of the foot (*Homan sign*); *absence of these findings does not exclude a diagnosis of DVT*.

*Pulmonary embolism* is a common and serious clinical complication of DVT (Chapter 4), resulting from fragmentation or detachment of the venous thrombus. In many cases, the first manifestation of thrombophlebitis is a pulmonary embolus. Depending on the size and number of emboli, the outcome can range from no symptoms at all to death.

### ***Superior and Inferior Vena Caval Syndromes***

The *superior vena caval syndrome* is usually caused by neoplasms that compress or invade the superior vena cava (e.g., bronchogenic carcinoma or mediastinal lymphoma). The resulting obstruction produces a characteristic clinical complex including marked dilation of the veins of the head, neck, and arms with cyanosis. Pulmonary vessels can also become compressed, inducing respiratory distress.

The *inferior vena caval syndrome* can be caused by neoplasms that compress or invade the inferior vena cava (IVC) or by a thrombus from the hepatic, renal, or lower extremity veins that propagates upward. Certain neoplasms-particularly hepatocellular carcinoma and renal cell carcinoma-show a striking tendency to grow within veins, and these may ultimately occlude the IVC. IVC obstruction induces marked lower extremity edema, distention of the superficial collateral veins of the lower abdomen, and-with renal vein involvement-massive proteinuria.

### ***Lymphangitis and Lymphedema***

Primary disorders of lymphatic vessels are extremely uncommon; secondary processes are much more common and develop in association with inflammation or malignancies.

*Lymphangitis* is the acute inflammation elicited when bacterial infections spread into and through the lymphatics; the most common agents are group A  $\beta$ -hemolytic streptococci, although any microbe can cause acute lymphangitis. The affected lymphatics are dilated and filled with an exudate of neutrophils and monocytes; these infiltrates can extend through the vessel wall into the perilymphatic tissues and, in severe cases, produce cellulitis or focal abscesses. Clinically, lymphangitis is recognized by red, painful subcutaneous streaks (the inflamed lymphatics), with painful enlargement of the draining lymph nodes (*acute lymphadenitis*). If bacteria are not contained within the lymph nodes, subsequent passage into the venous circulation can result in bacteremia or sepsis.

*Primary lymphedema* can occur as an isolated congenital defect (simple congenital lymphedema) or as the familial *Milroy disease (heredofamilial congenital lymphedema)*, resulting from lymphatic agenesis or hypoplasia. *Secondary or obstructive lymphedema* represents the accumulation of interstitial fluid behind a blockage of a previously normal lymphatic; such obstruction can result from

Malignant tumors obstructing either the lymphatic channels or the regional lymph nodes  
Surgical procedures that remove regional groups of lymph nodes (e.g., axillary lymph nodes in radical mastectomy)  
Postirradiation fibrosis  
Filariasis  
Postinflammatory thrombosis and scarring

Regardless of the cause, lymphedema increases the hydrostatic pressure in the lymphatics behind the obstruction and causes increased interstitial fluid. Persistence of this edema leads to increased deposition of interstitial connective tissue, with tissue expansion, *brawny induration* or *peau d'orange* appearance of the overlying skin, and eventually ulcers due to inadequate tissue perfusion. Milky accumulations of lymph in various spaces are designated *chylous ascites* (abdomen), *chylothorax*, and *chylopericardium*; these are caused by rupture of dilated lymphatics, typically obstructed secondary to an infiltrating tumor mass.



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## TUMORS

Tumors of blood vessels and lymphatics range from benign hemangiomas, to intermediate lesions infrequently metastatic, to relatively rare, highly malignant angiosarcomas (Table 10-5). Primary tumors of the artery, and vena cava) are extremely rare and are mostly connective tissue sarcomas. Congenital non-neoplastic reactive vascular proliferations (e.g., *bacillary angiomatosis*) can also present as tumors.

Vascular neoplasms can be derived from ECs (e.g., hemangioma, lymphangioma, angiosarcoma) and/or surround blood vessels (e.g., glomus tumor, hemangiopericytoma). Although a benign, well-organized tumor can be readily discriminated from an anaplastic, high-grade angiosarcoma, the distinction between the two can be difficult. General rules of thumb:

Benign tumors usually produce obvious vascular channels filled with blood cells (lymphatic space) lined by a monolayer of normal ECs, without atypia. Malignant tumors are more solidly cellular with cytologic atypia; they usually do not form well-organized vessels. The endothelial origin of neoplastic vessels can usually be confirmed by immunohistochemical demonstration of EC-specific markers such as CD31 and von Willebrand factor.

**Table 10-5. Classification of Vascular Tumors and Tumor-like Conditions**

<b>Benign Neoplasms, Developmental and Acquired Conditions</b>
Hemangioma
Capillary hemangioma
Cavernous hemangioma
Pyogenic granuloma
Lymphangioma
Simple (capillary) lymphangioma
Cavernous lymphangioma (cystic hygroma)
Glomus tumor
Vascular ectasias
Nevus flammeus
Spider telangiectasia (arterial spider)
Hereditary hemorrhagic telangiectasis (Osler-Weber-Rendu disease)
Reactive vascular proliferations
Bacillary angiomatosis
<b>Intermediate-Grade Neoplasms</b>
Kaposi sarcoma
Hemangioendothelioma
<b>Malignant Neoplasms</b>
Angiosarcoma
Hemangiopericytoma

Because vascular tumors result from dysregulated vascular proliferation, the possibility of controlling vessel formation (anti-angiogenic factors) is particularly exciting.

### Benign Tumors and Tumor-like Conditions

#### *Hemangioma*

Hemangiomas are very common tumors characterized by increased numbers of normal or abnormal blood vessels. They may be difficult to distinguish from vascular malformations. These lesions constitute 7% of all tumors (Chapter 7). Most are present from birth and expand along with the growth of the child, but many regress spontaneously. Although some hemangiomas can involve large portions of the body (called *angio*), most are superficial lesions, often of the head or neck, but they can occur internally, with nearly one-third of cases involving internal organs. Transformation occurs rarely, if at all. There are several histologic and clinical variants:

### Capillary Hemangioma

The most common variant, *capillary hemangiomas* occur in the skin, subcutaneous tissues, and mucous membranes of the mouth and lips, as well as in the liver, spleen, and kidneys. The "strawberry type," or *juvenile hemangioma*, is the most common (1 in 200 births) and may be multiple. It grows rapidly in the first few months but then fades and regresses by age 7 in 75% to 90% of cases.

#### Morphology

Capillary hemangiomas are bright red to blue and vary from a few millimeters to several centimeters in diameter; hemangiomas can be level with the surface of the skin or slightly elevated above the overlying epithelium (Fig. 10-29A). Histologically, these are unencapsulated aggregates of small, thin-walled capillaries, usually blood filled and lined by flattened endothelium; vessels are embedded in a loose connective tissue stroma (Fig. 10-29B). The lumina may be partially or completely occluded by red blood cells. Vessel rupture accounts for hemosiderin pigment in these lesions as well as for bleeding.

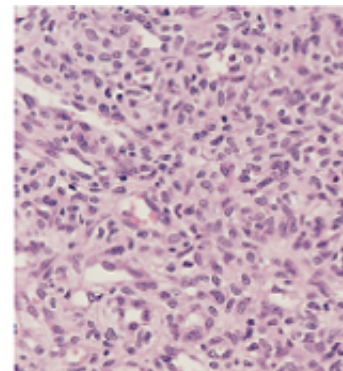
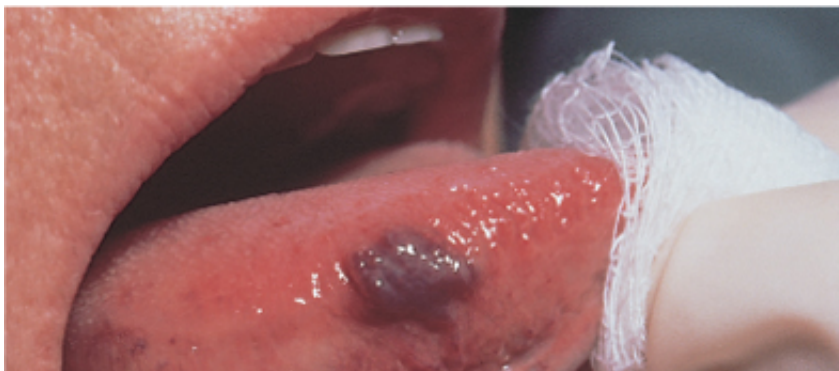
### Cavernous Hemangioma

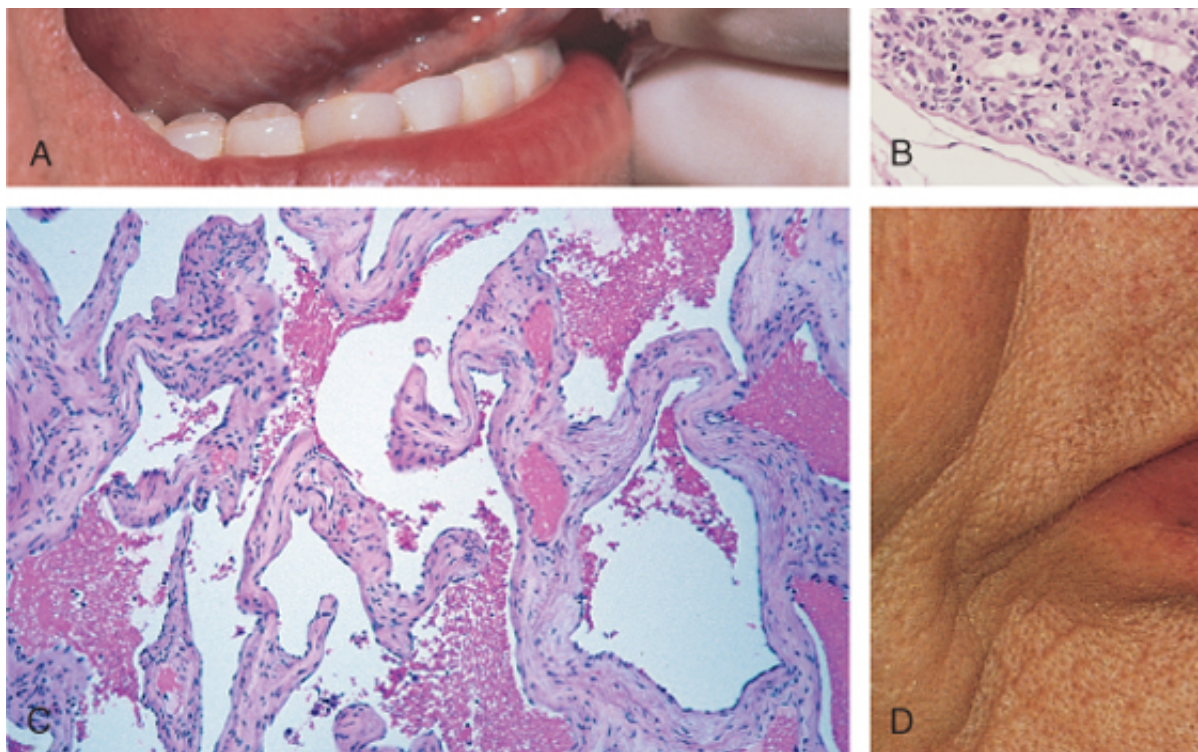
These are characterized by large, dilated vascular channels; compared with capillary hemangiomas, they are more circumscribed and more frequently involve deep structures. Because they may be locally destructive and do not regress, some may require surgery.

#### Morphology

Grossly, cavernous hemangiomas appear as red-blue, soft, spongy masses 1 to 2 cm in diameter. They can affect large subcutaneous areas of the face, extremities, or other body regions. The mass is sharply defined but not encapsulated, and it is composed of large, cavernous spaces separated by a mild-to-moderate amount of connective tissue stroma (Fig. 10-30A). Thrombosis with associated dystrophic calcification is common.

In most cases, the tumors are of little clinical significance; however, they can be a cosmetic problem and are vulnerable to traumatic ulceration and bleeding. Moreover, visceral hemangiomas must be distinguished from more ominous (e.g., malignant) lesions. The most problematic, because they can cause pressure symptoms or rupture, are the cavernous component of **von Hippel-Lindau disease** (Chapter 23), occurring within the cerebellum, retina, and eye grounds, along with similar angiomatous lesions or cystic neoplasms in the pancreas. The von Hippel-Lindau disease is also associated with renal neoplasms (Chapter 14).





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 Figure 10-29 Hemangiomas. **A**, Hemangioma of the tongue. **B**, Histology of juvenile capillary hemangioma. **C**, Histology of a pyogenic granuloma of the lip. (**A** and **D**, Courtesy of Dr. John Sexton, Beth Israel Hospital, Boston, Massachusetts. **B**, Courtesy of Dr. John Sexton, Beth Israel Hospital, Boston, Massachusetts. **C**, Courtesy of Dr. Thomas Rogers, University of Texas Southwestern Medical Center, Dallas, Texas.)

### **Pyogenic Granuloma**

This form of capillary hemangioma is a rapidly growing peduncular red nodule on the skin, gingiva, or mucosa, often ulcerated (Fig. 10-29D). Roughly a third of lesions develop after trauma, reaching a size of 1 cm. Proliferating capillaries are often accompanied by extensive edema and an acute and chronic inflammatory infiltrate, giving it a striking similarity to exuberant granulation tissue. *Pregnancy tumor* (granuloma gravidarum) is a pyogenic granuloma of the gingiva of 1% of pregnant women. These lesions can spontaneously regress (especially after pregnancy), but in some cases surgical excision is required. Recurrence is rare.

### **Lymphangioma**

Lymphangiomas are the benign lymphatic analogue of hemangiomas.

#### **Simple (Capillary) Lymphangioma**

These are composed of small lymphatic channels predominantly occurring in the head, neck, and chest. They are slightly elevated or sometimes pedunculated lesions that may reach 1 to 2 cm in diameter. Histologically, they consist of numerous small, thin-walled, endothelium-lined spaces that can be distinguished from capillary channels only by the absence of red blood cells.

#### **Cavernous Lymphangioma (Cystic Hygroma)**

These lesions are typically found in the neck or axilla of children and, rarely, in the retroperitoneum. They are common in Turner syndrome (Chapter 7). These lesions can occasionally be enormous ( $\leq 15$  cm) and produce gross deformities about the neck. Tumors are composed of massively dilated lymphatic channels separated by intervening connective tissue stroma containing lymphoid aggregates. The tumor margins are not encapsulated, making resection difficult.

#### **Glomus Tumor (Glomangioma)**

Glomus tumors are biologically benign but often exquisitely painful tumors arising from modified smooth muscle arteriovenous structure involved in thermoregulation. Although they can resemble cavernous hemangiomas, they are histologically distinct.

arteriovenous structure involved in thermoregulation. Although they can resemble cavernous hemangiomas, they are a distinct entity by virtue of their constituent cells. They are most commonly found in the distal portion of the fingers and toenails. Excision is curative.

### **Morphology**

Glomus tumors are round, slightly elevated, red-blue, firm nodules (generally 1-2 mm in diameter) that can initially resemble a minute focus of hemorrhage under the nail. Histologically, they consist of aggregates, nests, and masses of specialized glomus cells intimately associated with small blood vessels and channels, all within a connective tissue stroma. Individual tumor cells are small, uniform, and cuboidal, with scant cytoplasm and ultrastructural features similar to SMCs.

### **Vascular Ectasias**

*Vascular ectasias* are common lesions characterized by local dilation of preexisting vessels; the term is used for a congenital anomaly or acquired exaggeration of preformed vessels—usually in the form of capillaries, venules, and arterioles that creates a discrete red lesion.

#### *Nevus Flammeus*

This lesion is the ordinary "birthmark" and is the most common form of ectasia; it is characterized by a large, flat, red or purple patch ranging in color from light pink to deep purple. Histologically, there is only vascular dilation; most of the vessels are dilated.

The so-called *port wine stain* is a special form of nevus flammeus; these lesions tend to grow with age and demonstrate no tendency to fade. In most cases, the reason(s) for this distinct behavior of port wine stains is unknown. Lesions in a trigeminal nerve distribution are occasionally associated with the *Sturge-Weber syndrome* (also called *nevus flammeus*). Sturge-Weber syndrome is an uncommon congenital disorder with aberrant mesoderm associated with venous angiomatous masses in the cortical leptomeninges and ipsilateral facial port wine stain. It is associated with seizures, hemiplegia, and skull radio-opacities. Thus, *a large facial vascular malformation in a child is usually associated with more extensive vascular malformations.*

#### *Spider Telangiectasia*

This non-neoplastic vascular lesion grossly resembles a spider; there is a radial, often pulsatile arrangement of dilated arterioles (resembling legs) about a central core (resembling a body) that blanches when pressure is applied. It is seen on the face, neck, or upper chest and is most frequently associated with hyperestrogenic states. The mechanism by which elevated estrogen levels contribute to "spider" formation is not known.

#### *Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)*

In this autosomal dominant disorder, the telangiectasias are malformations composed of dilated capillaries. They are widely distributed over the skin and oral mucous membranes, as well as in the respiratory and gastrointestinal tracts. These lesions rupture, causing serious epistaxis (nosebleeds), GI bleeding, or hematuria.

### **Bacillary Angiomatosis**

*Bacillary angiomatosis* is an opportunistic infection in immunocompromised persons that manifests as a red, nodular, subcutaneous mass in bone, brain, and other organs; there is a closely related vascular lesion of liver and spleen called *pyoderma gangrenosum*. In patients with acquired immunodeficiency syndrome, bacillary angiomatosis is caused by infection with the *Bartonella* genus. Two species are implicated: *Bartonella henselae*, the organism responsible for the principal reservoir (cat scratch fever), and *B. quintana*, the cause of "trench fever" in World War I (the organism

### **Morphology**

Grossly, the skin lesions in bacillary angiomatosis are characterized by red papules or nodules. Histologically, there is capillary proliferation with prominent nuclear atypia and mitoses (Fig. 10-30). Lesions contain stromal neutrophils, nuclear debris, and granular material representing the causal bacteria.

Although difficult to cultivate in the laboratory, the causal organisms can be unequivocally demonstrated by immunofluorescence.



polymerase chain reaction and species-specific primers. Very recent evidence suggests that the induction of host tissue production of hypoxia-inducible factor 1, which in turn drives vascular endothelial growth factor (VEGF) production, is a key mechanism in the pathogenesis of Kaposi's sarcoma. The infections are cleared by macrolide antibiotics (including erythromycin<sup>®</sup>).

## Intermediate-Grade (Borderline Low-Grade Malignant) Tumors

### Kaposi Sarcoma

Though rare in other populations, Kaposi sarcoma (KS) used to be fairly common in patients with (AIDS) prior to the advent of effective antiretroviral therapy; indeed, its presence is used as a criterion for AIDS. While four forms of the disease are recognized (based on population demographics and risks), all share a common pathogenesis (see below):

*Chronic KS* (also called *classic* or *European KS*) was first described by Kaposi in 1872; it is found in Eastern European (especially Ashkenazi Jews) or Mediterranean descent and is uncommon in the United States. It can be associated with an underlying second malignancy or altered immunity, but is not associated with HIV. Chronic KS presents with multiple red to purple skin plaques or nodules, usually on the lower extremities, which slowly increase in size and number and spread more proximally. Though locally persistent, they do not metastasize and remain localized to the skin and subcutaneous tissue. *Lymphadenopathic KS* (also called *Burkitt lymphoma*) has a general geographic distribution as Burkitt lymphoma and is particularly prevalent among South African blacks associated with HIV. Skin lesions are sparse, and patients present instead with lymphadenopathy. *Transplant-associated KS* occasionally involves the viscera and is extremely aggressive. In combination with AIDS-associated KS, it is the most common tumor in central Africa (50% of all tumors in men in some countries). *Transplant-associated KS* occurs in solid-organ transplantation with its attendant long-term immunosuppression. It tends to be more aggressive, with mucosal and visceral involvement; cutaneous lesions may be absent. Lesions occasionally regress after immunosuppressive therapy is attenuated, but at the risk of organ rejection. *AIDS-associated (epidemic) KS* was first described in patients, particularly male homosexuals. However, with current regimens of intensive antiretroviral therapy, its incidence is now less than 1% (although it is still the most prevalent malignancy in AIDS patients in the United States). It involves lymph nodes and viscera, with wide dissemination early in the course of disease. Most patients are infected rather than from KS.



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Figure 10-30 Bacillary angiomatosis. **A**, Photograph of a moist, erosive cutaneous lesion. **B**, Histologic appearance of the lesion, showing a dense proliferation of small, dark-staining, round cells (neutrophils) within a vascular stroma. Inset, Demonstration by modified silver (Warthin-Starry) stain of clusters of tangled bacilli (Bartonella henselae). **B** and inset, Courtesy of Dr. Scott G. Johnson, Beth Israel Deaconess Medical Center, Boston, Massachusetts. (Massachusetts.)



## Pathogenesis

In 1994 a previously unrecognized herpesvirus (*human herpesvirus 8 [HHV-8]* or KS-associated herpesvirus) was identified in a cutaneous KS lesion in an AIDS patient. Indeed, regardless of the clinical subtype (described above), KS has subsequently been shown to be KSHV infected. Like Epstein-Barr virus, KSHV is a member of the  $\gamma$ -herpesvirinae subfamily and is transmitted sexually and by poorly understood nonsexual routes. The role of KSHV in the pathogenesis of KS and other manifestations of HIV infection.

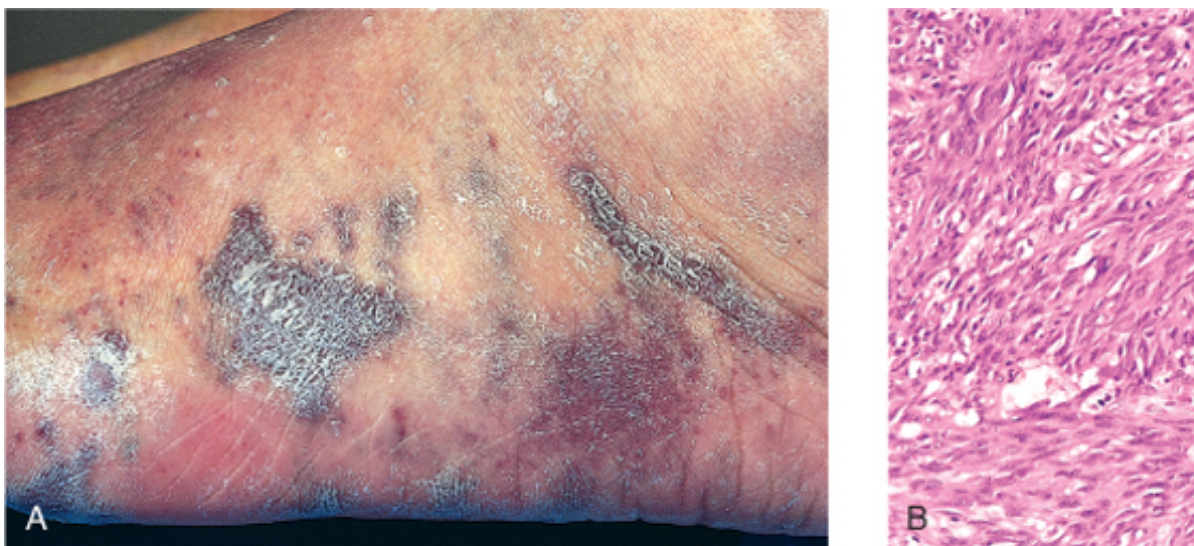
### Morphology

In the indolent, classic KS of older men (and sometimes in other variants), three stages are recognized: patch, plaque, and nodule.

**Patches** are solitary or multiple pink, red, or purple macules typically confined to the skin surface (Fig. 10-31A). Microscopic examination discloses only dilated, irregular, and angulated blood vessels (ECs) with an interspersed infiltrate of lymphocytes, plasma cells, and macrophages (some containing hemosiderin). These lesions are difficult to distinguish from granulation tissue.

With time, lesions spread proximally and convert into larger, violaceous, raised **plaques** composed of dermal accumulations of dilated, jagged vascular channels lined by proliferating endothelial cells. Scattered between the vascular channels are sheets of plump, proliferating spindle cells. Scattered between the vascular channels are cells (escaping from leaky vessels), hemosiderin-laden macrophages, lymphocytes, and hyaline globules of uncertain nature may be found in the spindle cell areas.

At a still later stage, lesions become **nodular** and more distinctly neoplastic. These nodules are composed of sheets of plump, proliferating spindle cells, mostly in the dermis or subcutaneous tissue, encompassing small vessels and slitlike spaces containing rows of red cells. More prominent is the hemosiderin pigment, lymphocytes, and occasional macrophages are seen; mitotic figures are the round, pink, cytoplasmic globules. The nodular stage is often accompanied by ulceration, particularly in the African and AIDS-associated variants.



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Figure 10-31 Kaposi sarcoma. **A**, Gross photograph, illustrating coalescent red-purple macules and plaques of the skin. **B**, Microscopic image, demonstrating sheets of plump, proliferating spindle cells and vascular spaces. (Courtesy of Dr. Christopher D.M. Fennell, Boston, Massachusetts.)

### Clinical Course

The course of KS varies widely and is significantly affected by the clinical setting. Most primary KS is—at least initially—largely restricted to the surface of the body, and surgical resection is usually

Radiation can be used for multiple lesions in a restricted area, and chemotherapy yields satisfactory results. Lymphadenopathic KS can also be treated with chemotherapy or radiotherapy with good results. Following withdrawal of immunosuppression (perhaps with adjunct chemotherapy or radiotherapy) is often effective. Antiretroviral therapy for HIV is usually helpful, with or without therapy targeted to the KS lesions. These approaches have also proved somewhat effective.

### **Hemangioendothelioma**

Hemangioendothelioma denotes a wide spectrum of vascular neoplasms with histology and clinical behavior ranging from benign, well-differentiated hemangiomas and frankly anaplastic angiosarcomas (see below).

*Epithelioid hemangioendothelioma* is an example of this group; it is a vascular tumor of adults occurring in soft tissue and bone. The tumor cells are plump and often cuboidal (resembling epithelial cells); well-defined vascular channels are present. The differential diagnosis includes other epithelioid tumors including metastatic carcinoma, melanoma, and epithelioid sarcoma. The prognosis is variable; most are cured by excision, but up to 40% recur, 20% to 30% eventually metastasize, and 10% to 20% die of the disease.

### **Malignant Tumors**

#### **Angiosarcoma**

*Angiosarcomas* are malignant endothelial neoplasms (Fig. 10-32) with histology varying from high-grade hemangiomas (*hemangiosarcoma*) to anaplastic lesions difficult to distinguish from carcinomas or sarcomas. They are commonly affected, with equal gender predilections; they occur at any site but most often involve the liver.

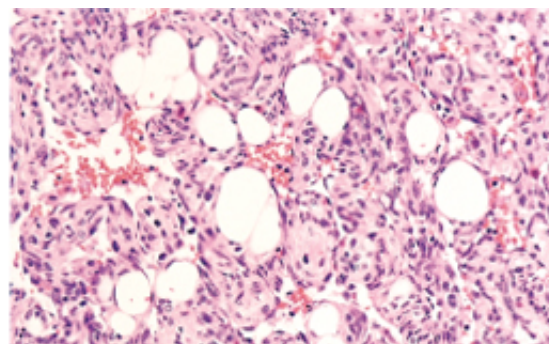
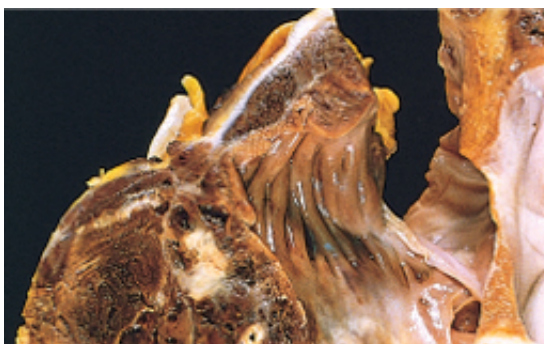
*Hepatic angiosarcomas* are associated with carcinogenic exposures, including arsenic (arsenical contrast agent formerly used for radiologic imaging), and polyvinyl chloride (PVC; a widely used plastic). There is a long latency between initial exposure and eventual tumor development. The increased frequency of these tumors is one of the truly well-documented instances of human chemical carcinogenesis.

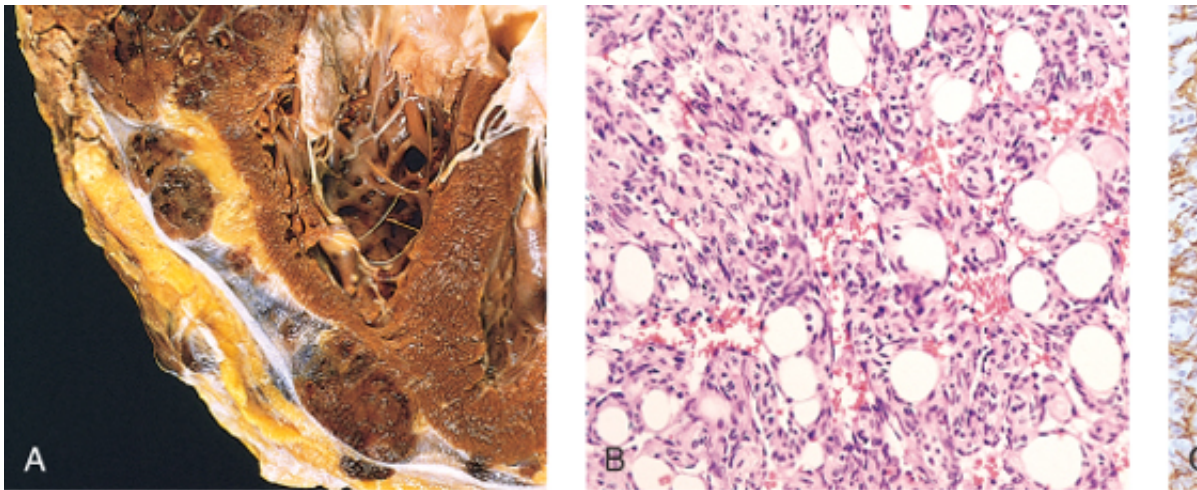
Angiosarcomas can also arise in the setting of lymphedema, classically in the ipsilateral upper extremity following mastectomy (i.e., with lymph node resection) for breast cancer; the tumor presumably arises from the lymphatics. Angiosarcomas can also be induced by radiation and are associated with foreign material introduced accidentally.

#### **Morphology**

Cutaneous angiosarcomas can begin as deceptively small, sharply demarcated, as red nodules; most eventually become large, fleshy masses of red-tan to gray-white. The margins blend imperceptibly with surrounding structures. Central areas of necrosis are frequent.

Microscopically, all degrees of differentiation can be seen, from plump, anaplastic cells producing vascular channels (see Fig. 10-32B) to wildly undifferentiated tumors having a sarcomatous appearance and producing no definite blood vessels. The EC origin of these tumors is supported by immunohistochemical staining with CD31 or von Willebrand factor (see Fig. 10-32C).





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 Figure 10-32 Angiosarcoma. **A**, Gross photograph of angiosarcoma of the heart (right ventricle). **B**, Photomicrograph with dense clumps of irregular, moderate anaplastic cells and distinct vascular lumens. **C**, Positive immunohistochemical marker CD31, proving the endothelial nature of the tumor cells.

Clinically, angiosarcomas are locally invasive and can metastasize readily. Although patients with quite poorly, current 5-year survival rates approach 30%.

### ***Hemangiopericytoma***

Hemangiopericytomas are rare tumors derived from pericytes-myofibroblast-like cells that are not venules. Hemangiopericytomas can occur as slowly enlarging, painless masses at any anatomic site, especially lower extremities (especially the thigh) and in the retroperitoneum. They consist of numerous branching sinusoidal spaces enclosed within nests of spindle-shaped to round cells. Special stains confirm the basement membrane and are therefore pericytes. The tumors may recur after excision, and may metastasize hematogenously to lungs, bone, or liver.

### **SUMMARY** **Vascular Tumors**

Neoplasms of vessels can derive from either blood vessels or lymphatics, a mesenchymal (hemangioma, lymphangioma, angiosarcoma) or vascular support cells (hemangiopericytoma). Vascular tumors are predominantly benign (e.g., hemangioma), intermediate, locally aggressive lesions (e.g. Kaposi sarcoma), or rarely, highly malignant (e.g. angiosarcoma). Benign tumors usually form obvious vascular channels lined by a single layer of endothelial cells. Malignant tumors are more typically solid and cellular, without well-organized vascular channels and show significant cytologic atypia.

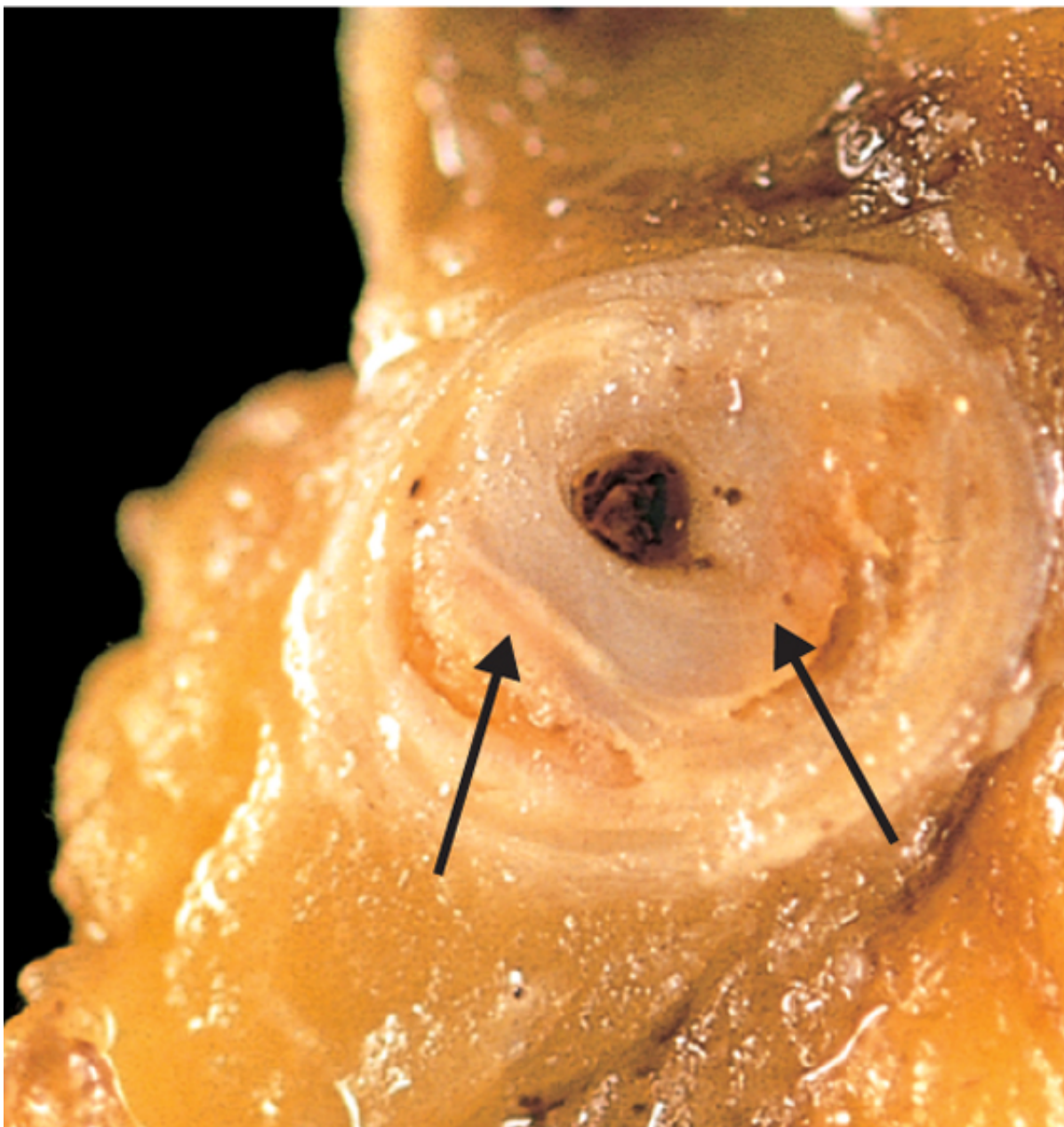


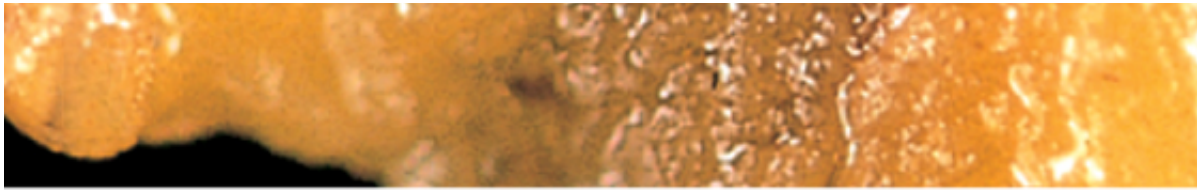


## PATHOLOGY OF VASCULAR INTERVENTION

The morphologic changes that occur in vessels following therapeutic intervention (i.e., balloon angioplasty, a stent), vascular thrombosis (after angioplasty), and abnormal mechanical forces (e.g., a saphenous vein arterial circulation as a coronary artery bypass graft) all elicit similar responses characteristic of vascular remodeling. In atherosclerosis, the traumas of vascular intervention tend to induce a concentric intimal thickening and their associated matrix deposition (Fig. 10-33).

### ***Endovascular Stenting***





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Figure 10-33 Gross photograph of restenosis subsequent to balloon angioplasty, demonstrating residual atherosclerotic plaque and a glistening proliferative lesion (right arrow).

Coronary stents are expandable tubes of metallic mesh that are inserted to preserve luminal patency in the presence of arterial stenoses; stents are used fairly routinely in all angioplasty procedures. Stents provide a permanent lumen, "tack down" the intimal flaps and vascular dissections that occur during angioplasty, and prevent restenosis. Nevertheless, both early thrombosis and late intimal thickening can occur within stents, and restenosis much like that seen with angioplasty alone (Fig. 10-33). Potent antithrombotic agents (aspirin, clopidogrel) are used to minimize thrombosis, and the newest generation of stents release antiproliferative drugs (e.g., sirolimus, paclitaxel). These combined interventions result in markedly diminished intimal hyperplasia.

### Vascular Replacement

Synthetic or autologous vascular grafts are increasingly used to replace damaged vessels or bypass occluded arteries. Synthetic grafts, large-bore (12- to 18-mm) conduits function well in high-flow locations such as the aorta. Small artificial grafts ( $\leq 8$  mm in diameter) generally fail because of acute thrombosis.

Consequently, for coronary artery bypass surgery (>400,000 per year in the United States), grafts of reversed autologous saphenous vein (taken from the patient's own leg) or left internal mammary artery (anastomosed to the heart). The long-term patency of saphenous vein grafts is only 50% at 10 years; grafts occlude (typically early), intimal thickening (months to years postoperatively), and graft atherosclerosis-sometimes leading to plaque rupture, thrombi, or aneurysms (usually more than 2 to 3 years). In contrast, more than 90% of internal mammary artery grafts are patent at 10 years.

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## 11 The Heart\*

In addition to its historical association with human emotions (as well as compassion, strength, and resolve—indeed, Aristotle felt it was the seat of the soul!), the heart is a vitally life-sustaining organ; it is responsible for pumping more than 6000 liters of blood daily through the body. In its normal, healthy state, the heart perfuses tissues with a steady supply of vital nutrients and facilitates the removal of waste products. When pathology supervenes, cardiac dysfunction is associated with devastating physiologic consequences. Heart disease remains the leading cause of morbidity and mortality in industrialized nations; it accounts for nearly 40% of all postnatal deaths in the United States, totaling about 750,000 individuals annually (nearly twice the number of deaths caused by all forms of cancer combined). The yearly economic burden of ischemic heart disease (IHD) alone is in excess of \$100 billion.

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In this chapter we will first review the salient features of congestive heart failure (CHF), the common end point of many cardiac diseases. This will be followed by a discussion of the major categories of cardiac disease including selected congenital heart diseases, IHD (coronary artery disease), hypertensive heart disease, heart disease caused by intrinsic pulmonary diseases (*cor pulmonale*), valvular heart disease, and primary myocardial disease. A few highlights about pericardial disease and cardiac neoplasms are also presented before we conclude with a brief look at cardiac transplantation.



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## HEART FAILURE

Heart failure (also called *congestive heart failure*, or *CHF*) is a frequent end point of many of the conditions mentioned above. In the United States alone, CHF affects nearly 5 million individuals annually, necessitating >1 million hospitalizations, and contributes to death of 300,000 patients a year. Most heart failure is the consequence of *systolic dysfunction*, the progressive deterioration of myocardial contractile function; this is most commonly due to ischemic heart disease or hypertension. However, in 20% to 50% of patients the heart contracts normally but relaxation is abnormal. These patients with "diastolic" failure are generally older and more likely to be female with hypertension or diabetes mellitus. Heart failure may be caused by valve failure (e.g., endocarditis) or can also occur in normal hearts suddenly burdened with an abnormal load (e.g., fluid or pressure overload).

In heart failure, the heart is unable to pump blood at a rate that meets the requirements of the metabolizing tissues, or can only do so only with filling pressures that are higher than normal. Onset may be insidious or acute. In most cases of CHF the heart cannot keep pace with basic peripheral demands; in a minority of cases, heart failure results from greatly increased tissue demands for blood (*high-output failure*). Excluded from the definition are conditions in which inadequate cardiac output occurs because of blood loss or some other process that impairs blood return to the heart.

In a mechanical sense, the failing heart in CHF can no longer pump the blood delivered to it by the venous circulation. Inadequate cardiac output-called *forward failure*-is almost always accompanied by increased congestion of the venous circulation (*backward failure*), because the failing ventricle is unable to eject the venous blood delivered to it. This results in an increased end-diastolic ventricular volume, leading to increased end-diastolic pressures and, finally, elevated venous pressures. Although the root problem in CHF is typically abnormal cardiac function, virtually every other organ is eventually affected by some combination of forward and backward failure.

The cardiovascular system can adapt to reduced myocardial contractility or increased hemodynamic burden by a few different pathways. The most important are

*Activation of neurohumoral systems*, especially (1) release of the neurotransmitter norepinephrine by the sympathetic nervous system (increases heart rate and augments myocardial contractility and vascular resistance), (2) activation of the renin-angiotensin-aldosterone system, and (3) release of atrial natriuretic peptide (ANP). This is a polypeptide hormone secreted by the atria in the setting of atrial distension. It causes vasodilation, natriuresis, and diuresis that help alleviate volume or pressure overload states. *The Frank-Starling mechanism*. As cardiac failure progresses, end-diastolic pressures increase, causing individual cardiac muscle fibers to stretch; this ultimately increases the volume of the cardiac chamber. In accordance with the Frank-Starling relationship, these lengthened fibers initially contract more forcibly, thereby increasing cardiac output. If the dilated ventricle is able to maintain cardiac output at a level that meets the needs of the body, the patient is said to be in *compensated heart failure*. However, increasing dilation increases ventricular wall tension, which increases the oxygen requirements of an already compromised myocardium. With time, the failing myocardium is no longer able to propel sufficient blood to meet the needs of the body, even at rest. At this point, patients enter a phase termed *decompensated heart failure*. *Myocardial structural changes, including augmented muscle mass (hypertrophy)*, to increase the mass of contractile tissue. Because adult cardiac myocytes cannot proliferate, adaptation to a chronically increased workload involves

hypertrophy of individual muscle cells. In pressure overload states (e.g., hypertension, valvular stenosis), the hypertrophy is characterized by increased diameter of individual muscle fibers. This yields *concentric hypertrophy*, in which the thickness of the ventricular wall increases without an increase in the size of the chamber. In volume overload states (e.g., valvular regurgitation or abnormal shunts), it is the length of individual muscle fibers that increases. This results in *eccentric hypertrophy*, characterized by an increase in heart size as well as an increase in wall thickness.

Initially, these adaptive mechanisms may be adequate to maintain cardiac output in the face of declining cardiac performance. However, with sustained or worsening heart function, pathologic changes may eventually supervene, resulting in structural and functional disturbances; such degenerative changes include myocyte apoptosis, cytoskeletal alterations, and altered extracellular matrix synthesis and remodeling. Even hypertrophy comes at a significant cost to the cell. Oxygen requirements of the hypertrophic myocardium are increased as a result of increased myocardial cell mass and increased tension of the ventricular wall. Because the myocardial capillary bed does not always increase in step with the increased oxygen demands of the hypertrophic muscle fibers, the myocardium becomes vulnerable to *ischemic* injury.

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Heart failure can affect predominantly the left side or the right side, or both sides of the heart. The most common causes of left-sided cardiac failure are (1) IHD, (2) systemic hypertension, (3) mitral or aortic valve disease, and (4) primary diseases of the myocardium. The most common cause of right-sided heart failure is left ventricular failure, with its associated pulmonary congestion and elevation in pulmonary arterial pressure. Right-sided failure can also occur in the absence of left-sided heart failure in patients with intrinsic diseases of the lung parenchyma and/or pulmonary vasculature (cor pulmonale) and in patients with primary pulmonic or tricuspid valve disease. It sometimes follows congenital heart diseases, i.e., in the setting of left-to-right shunts with chronic volume and pressure overloads.

### Left-Sided Heart Failure

The morphologic and clinical effects of left-sided CHF primarily result from progressive damming of blood within the pulmonary circulation and the consequences of diminished peripheral blood pressure and flow.

#### Morphology

Findings in the heart depend on the underlying disease process; for example, myocardial infarction or valvular deformities may be present. Except in cases of mitral valve stenosis (or other processes that restrict left ventricular size), the left ventricle is usually **hypertrophied** and often **dilated**, sometimes quite massively. There are usually nonspecific changes of hypertrophy and fibrosis in the myocardium. Secondary enlargement of the left atrium with resultant atrial fibrillation (i.e., uncoordinated, chaotic contraction of the atrium) can reduce stroke volume or lead to blood stasis and **thrombus formation** (particularly in the atrial appendage); a fibrillating left atrium carries a substantially increased risk of embolic stroke. The extracardiac effects of left-sided heart failure are manifested most prominently in the lungs.

Rising pressure in the pulmonary veins is ultimately transmitted retrogradely to the capillaries, resulting in **pulmonary congestion and edema**. The lungs are heavy and boggy, and histologically there are perivascular and interstitial transudate, alveolar septal edema, and intra-alveolar edema (see also [Chapters 4](#) and [13](#)). Moreover, capillary leakiness leads to the accumulation of erythrocytes (containing



hemoglobin) that are phagocytosed by macrophages. Within macrophages, hemoglobin is converted to hemosiderin and hence hemosiderin-containing macrophages in the alveoli (called **heart failure cells**) are evidence of prior of pulmonary edema.

### *Clinical Features*

*Dyspnea* (breathlessness) is usually the earliest and most significant complaint of patients in left-sided heart failure; cough is also a common accompaniment of left heart failure due to fluid transudation into airspaces. With further cardiac impairment, patients develop dyspnea when recumbent (so-called *orthopnea*); this occurs because of increased venous return from the lower extremities and by elevation of the diaphragm when in the supine position. Orthopnea is typically relieved by sitting or standing, so that such patients usually sleep while sitting upright. *Paroxysmal nocturnal dyspnea* is a particularly dramatic form of breathlessness awakening patients from sleep with attacks of extreme dyspnea bordering on suffocation.

Other manifestations of left ventricular failure include an enlarged heart (cardiomegaly), tachycardia, a third heart sound ( $S_3$ ), and fine rales at the lung bases, produced by respirations through edematous pulmonary alveoli. With progressive ventricular dilation, the papillary muscles are displaced laterally, causing mitral regurgitation and a systolic murmur. Subsequent chronic dilation of the left atrium is often associated with *atrial fibrillation*, manifested by an "irregularly irregular" heartbeat.

### **Right-Sided Heart Failure**

Right-sided heart failure is usually the consequence of left-sided heart failure; any pressure increase in the pulmonary circulation inevitably produces an increased burden on the right side of the heart. Isolated right-sided heart failure is less common and it occurs in patients with intrinsic disease of lung parenchyma and/or pulmonary vasculature that result in chronic pulmonary hypertension (cor pulmonale). It can also occur in patients with pulmonic or tricuspid valve disease. Congenital heart diseases with right-to-left shunt can cause isolated right-sided heart failure, as well. Hypertrophy and dilation are generally confined to the right ventricle and atrium, although bulging of the ventricular septum to the left can cause dysfunction of the left ventricle.

The major morphologic and clinical effects of pure right-sided heart failure differ from those of left-sided heart failure in that pulmonary congestion is minimal, whereas engorgement of the systemic and portal venous systems is typically pronounced.

### **Morphology**

**Liver and Portal System.** The liver is usually increased in size and weight (congestive hepatomegaly), and a cut section displays prominent passive congestion, a pattern referred to as **nutmeg liver** (see [Chapter 4](#)); congested red centers of the liver lobules are surrounded by paler, sometimes fatty, peripheral regions. In some instances, especially when left-sided heart failure is also present, severe central hypoxia produces **centrilobular necrosis** along with the sinusoidal congestion. With long-standing severe right-sided heart failure, the central areas can become fibrotic, creating so-called **cardiac cirrhosis** ([Chapter 16](#)).

Right-sided heart failure also leads to elevated pressure in the portal vein and its tributaries. Congestion produces a tense, enlarged spleen (**congestive splenomegaly**). With long-standing congestion, the enlarged spleen can achieve weights of 300 to 500 gm (normal <150 gm). Microscopically, there can be marked sinusoidal dilation. Chronic edema of the bowel wall may interfere with absorption of nutrients. Accumulations of transudate in the peritoneal cavity can cause ascites.

**Pleural and Pericardial Spaces.** Fluid may accumulate in the pleural space (particularly right) and pericardial space (effusions). Thus, while pulmonary edema indicates left-sided heart failure, pleural effusions accompany both right-sided and left-sided heart failure. Pleural effusions (typically serous) can range from 100 mL to well over 1 L and can cause partial atelectasis of the affected lung. Unlike inflammatory edema, the edema fluid in CHF has a low protein content.

**Subcutaneous Tissues.** Peripheral edema of dependent portions of the body, especially ankle (pedal) and pretibial edema, is a hallmark of right-sided heart failure. In chronically bedridden patients, the edema may be primarily presacral. Generalized massive edema is called **anasarca**.

### *Clinical Features*

While the symptoms of left-sided heart failure are largely due to pulmonary congestion and edema, pure right-sided heart failure typically causes very few respiratory symptoms. Instead, there is systemic and portal venous congestion, with hepatic and splenic enlargement, peripheral edema, pleural effusion, and ascites. It is worth emphasizing, however, that in most cases of chronic cardiac decompensation, patients present with *biventricular CHF*, encompassing the clinical syndromes of both right-sided and left-sided heart failure. As CHF progresses, patients can become frankly cyanotic and acidotic, as a result of decreased tissue perfusion.

### **SUMMARY Heart Failure**

CHF occurs when the heart is unable to pump blood at a rate that meets the metabolic requirements of the peripheral tissue; inadequate cardiac output is usually accompanied by increased congestion of the relevant venous circulation. Left-sided heart failure is most commonly due to IHD, systemic hypertension, mitral or aortic valve disease, and primary diseases of the myocardium; symptoms are primarily related to pulmonary congestion and edema. Right-sided heart failure is most commonly due to left-sided heart failure or to primary pulmonary diseases; it is associated with peripheral edema and visceral congestion.





## CONGENITAL HEART DISEASE

Congenital heart diseases are abnormalities of the heart or great vessels that are present at birth. embryogenesis during gestational weeks 3 through 8, when major cardiovascular structures develop encompass a broad spectrum of defects, ranging from severe anomalies that cause death in the perinatal period to those that produce only minimal symptoms, even in adult life. Although figures vary, a generally accepted incidence of congenital heart disease is higher in premature infants and in stillborns. As might be expected, congenital heart disease is the leading cause of death among children.

Because of clinical advances, the number of patients surviving with congenital heart disease is increasing. It is estimated that 750,000 adults with congenital heart disease. Although surgery can correct the hemodynamic abnormalities, the heart may still not be completely normal. Myocardial hypertrophy and a cardiac remodeling brought about by the surgery are irreversible. Although adaptive initially, such changes can elicit late-onset arrhythmias, ischemia, and heart failure many years after surgery.

### *Pathogenesis*

General concepts regarding the etiology of congenital malformations were discussed in [Chapter 7](#). Factors relevant to congenital cardiac disease, keeping in mind that the cause is unknown in almost 90% of cases, include congenital rubella infection, are causal in many instances. *Genetic factors* are also clearly involved in congenital heart disease and by well-defined associations with certain chromosomal abnormalities (e.g., Down syndrome, Turner syndrome).

Cardiac morphogenesis involves multiple genes and is tightly regulated to ensure an effective embryonic development. It specifies cardiac cell fate, morphogenesis and looping of the heart tube, segmentation and growth, and connection of the great vessels to the heart. The molecular pathways controlling these processes are the foundation for understanding the basis of some congenital heart defects. Several congenital heart defects are caused by mutations in transcription factors. Mutations of the TBX5 transcription factor cause the atrial and ventricular septal defects. Mutations in the transcription factor NKX2.5 are associated with isolated atrial septal defects.

Since different cardiac structures can share the same developmental pathways, dissimilar lesions can result from a common genetic defect. The unifying feature of many outflow tract defects is the abnormal development of the neural crest cells whose migration into the embryonic heart is required for outflow tract formation. In particular, genes that play a major role in forming the conotruncus, the branchial arches, and the human face; we now know that these genes underlie 15% to 50% of outflow tract abnormalities. Moreover, these deletions can also cause developmental defects of the branchial arch and derivatives of the third and fourth pharyngeal pouches leading to thymic and parathyroid hypoplasia and immune deficiency (Di George syndrome, [Chapter 5](#)) and hypocalcemia.

**Table 11-1. Frequencies of Congenital Cardiac Malformations\***

Malformation	Incidence per Million Live Births
Ventricular septal defect	4482
Atrial septal defect	1043
Pulmonary stenosis	836
Patent ductus arteriosus	781
Tetralogy of Fallot	577
Coarctation of aorta	492
Atrioventricular septal defect	396
Aortic stenosis	388
Transposition of great arteries	388

Truncus arteriosus	136
Total anomalous pulmonary venous connection	120
Tricuspid atresia	118
TOTAL	9757

\*Presented as upper quartile of 44 published studies. Percentages do not add to 100% owing to rounding.  
Source: Hoffman JIE, Kaplan S: The incidence of congenital heart disease. J Am Coll Cardiol 39:1890, 2002.

Twelve disorders account for 85% of congenital heart disease; their frequencies are shown in [Table 11-1](#). Congenital heart diseases can be subdivided into three major groups:

Malformations causing a *left-to-right shunt* Malformations causing a *right-to-left shunt* (cyanotic diseases) Malformations causing *obstruction*

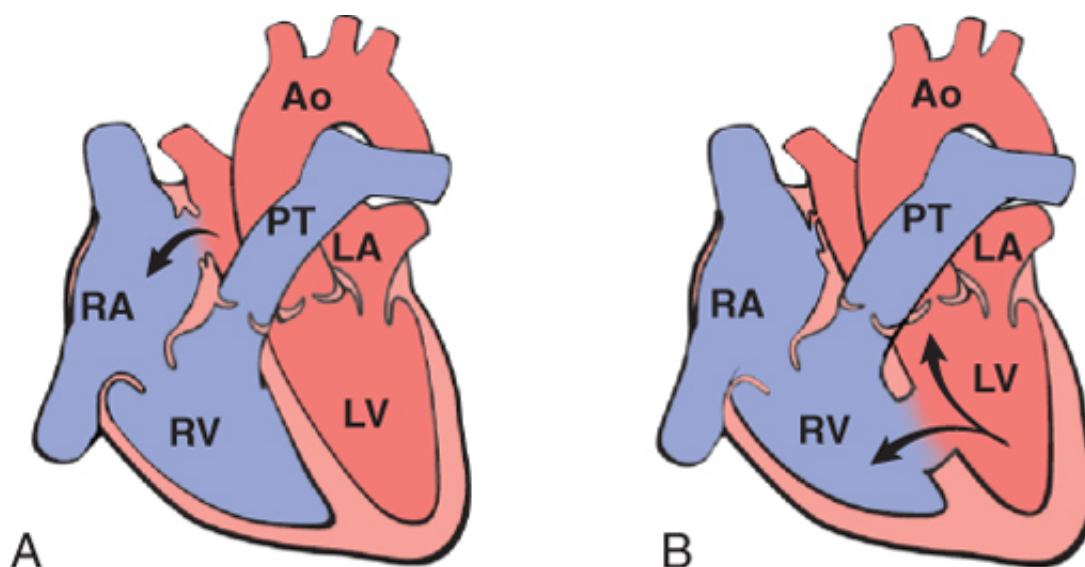
A *shunt* is an abnormal communication between chambers or blood vessels. Depending on pressure of blood from the left heart to the right heart (or vice versa). When there is a *right-to-left shunt*, a *d* results because the pulmonary circulation is bypassed and poorly oxygenated blood enters the systemic circulation. *Right-to-left shunts* increase pulmonary blood flow and are not associated (at least initially) with cyanosis. However, increased resistance to pulmonary circulation to increased pressure and volume, resulting in right ventricular failure. Some developmental anomalies obstruct vascular flow by narrowing the chambers, valves, or vessels, called *obstructive congenital heart disease*. A complete obstruction is called an *atresia*. In some disorders (pulmonary stenosis) is associated with a shunt (right-to-left through a ventricular septal defect [VSD]).

### Left-to-Right Shunts

Left-to-right shunts represent the most common type of congenital cardiac malformation (Fig. 11-1). They include atrial septal defects, ventricular septal defects, and *patent ductus arteriosus*. Atrial septal defects are typically associated with increased pulmonary blood flow. Ventricular septal defects and patent ductus arteriosus result in both increased pulmonary blood flow and increased left ventricular pressure. Left-to-right shunts can be asymptomatic or can cause fulminant CHF at birth.

*Cyanosis is not an early feature* of these defects, but it can occur late, after prolonged left-to-right shunt. Such reversal of flow and shunting of unoxygenated blood to the systemic circulation is called *right-to-left shunt*. When significant pulmonary hypertension develops, the structural defects of congenital heart disease are the rationale for early intervention, either surgical or nonsurgical.

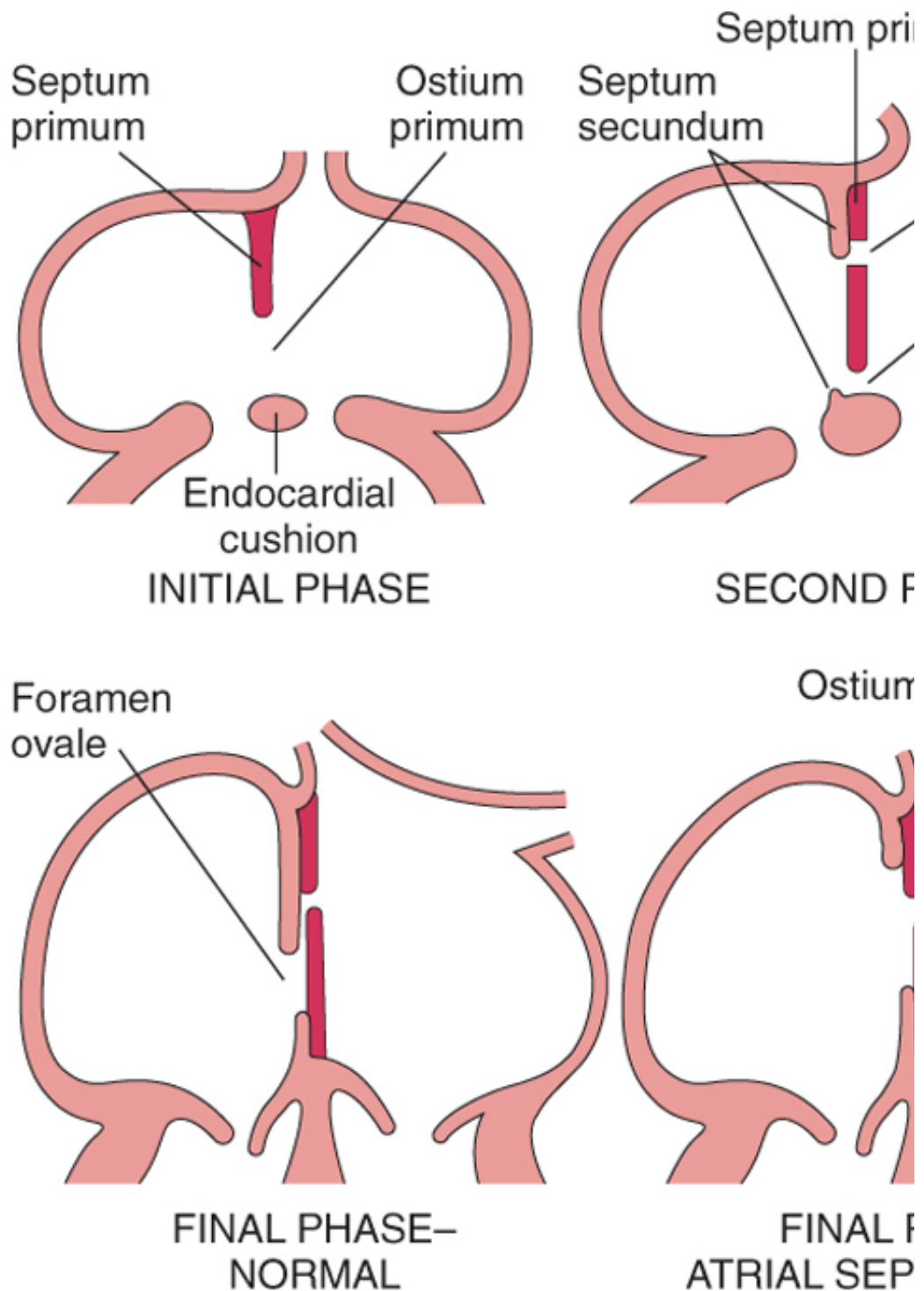
### Atrial Septal Defects



## ASD

## VSD

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 Figure 11-1 Congenital left-to-right shunts (see arrows). **A**, Atrial septal defect (ASD). **B**, Ventricular septal defect (VSD). In both conditions, pressures are the same in both ventricles. Pressure hypertrophy of the right ventricle and volume hypertrophy of the left ventricle lead to pulmonary hypertension and ductus arteriosus (PDA).



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 Figure 11-2 Embryogenesis of an atrial septal defect (ostium secundum type). The right atrium is to the left, and the left atrium is to the right.



Figure 11-2 Embryogenesis of an atrial septal defect, secundum secundum type. The right atrium is

ASDs are perhaps best understood from the perspective of normal atrial septation (Fig. 11-2). The *septum primum* from the dorsal wall of the common atrial chamber toward the developing *endostium primum*, initially separates the two. Continued growth and fusion of the septum with the endostium primum; however, a second opening, *ostium secundum*, now appears in the central atrial septum to allow continued flow of oxygenated blood from the right to left atria, essential for fetal life). As the *ostium secundum* makes its appearance adjacent to the septum primum. This septum secundum proliferates, overlapping a space termed the *foramen ovale*. The foramen ovale is closed on its left side by a flap of septum; this flap acts as a one-way valve that allows right-to-left blood flow during intrauterine life. As vascular resistance and rising systemic arterial pressure causes left atrial pressures to exceed the right atrial pressures, the functional closure of the foramen ovale. In most individuals the foramen ovale is permanently sealed by the development of secondary septa, although a minor degree of patency persists in about 25% of the general population.

Abnormalities in this sequence result in the development of the various ASDs; three types are recognized: *ostium secundum ASD*, which occurs when the septum secundum does not enlarge sufficiently to close the *ostium secundum*; *ostium primum ASDs* are less common (5% of cases); these occur if the septum primum and endostium primum do not fuse properly; and *sinus venosus ASDs* (5% of cases) are located near the entrance of the superior vena cava and have been associated with abnormal development of the NKX2.5 transcription factor.

### Morphology

**Ostium secundum ASDs** are typically smooth-walled defects near the foramen ovale and are often associated with other cardiac abnormalities. Because of the left-to-right shunt, hemodynamic consequences are accompanied by right atrial and ventricular dilation, right ventricular hypertrophy, and dilation of the pulmonary artery, reflecting the effects of a chronically increased volume load on the right heart. **Ostium primum ASDs** occur at the lowest part of the atrial septum and can extend to the atrioventricular valves, reflecting the close relationship between development of the septum primum and the endocardial cushion. Abnormalities of the atrioventricular valves are usually present, typically involving the anterior leaflet of the mitral valve or septal leaflet of the tricuspid valve. In more severe cases, a large primum defect is accompanied by a VSD and severe mitral and tricuspid valve defects. **Sinus venosus ASDs** are located high in the atrial septum and are often accompanied by anomalous drainage of the pulmonary veins into the right atrium or common atrioventricular canal.

### Clinical Features

Although VSDs are the most common congenital malformations at birth (Table 11-1), many of the ASDs (which are less likely to spontaneously close) are the most common defects to be first diagnosed. ASDs result in left-to-right shunts, as a result of the lower pressures in the pulmonary circulation and right side of the heart. Small ASDs are often tolerated, especially if they are less than 1 cm in diameter; even larger lesions do not usually produce symptoms. However, pulmonary vascular resistance can increase, resulting in pulmonary hypertension. The objectives of surgical closure of ASDs are the reversal of the hemodynamic consequences, including heart failure, paradoxical embolization, and irreversible pulmonary vascular disease. Postoperative survival is comparable to that of a normal population. Ostium primum defects are more common in patients with CHF, in part because of the high frequency of associated mitral insufficiency.

### Ventricular Septal Defects

Incomplete closure of the ventricular septum allows left-to-right shunting and is the most common congenital cardiac malformation (Table 11-1 and Fig. 11-1B). The ventricular septum is normally formed by the fusion of an intraventricular septum that grows upward from the apex of the heart with a thinner membranous partition that grows downward from the septum primum. The membranous region is the last part of the septum to develop and is the site of approximately 90% of VSDs. At birth, most VSDs close spontaneously in childhood, so that the overall incidence in adults is about 1%. About 30% of VSDs occur in isolation; more commonly, they are associated with other cardiac malformations.

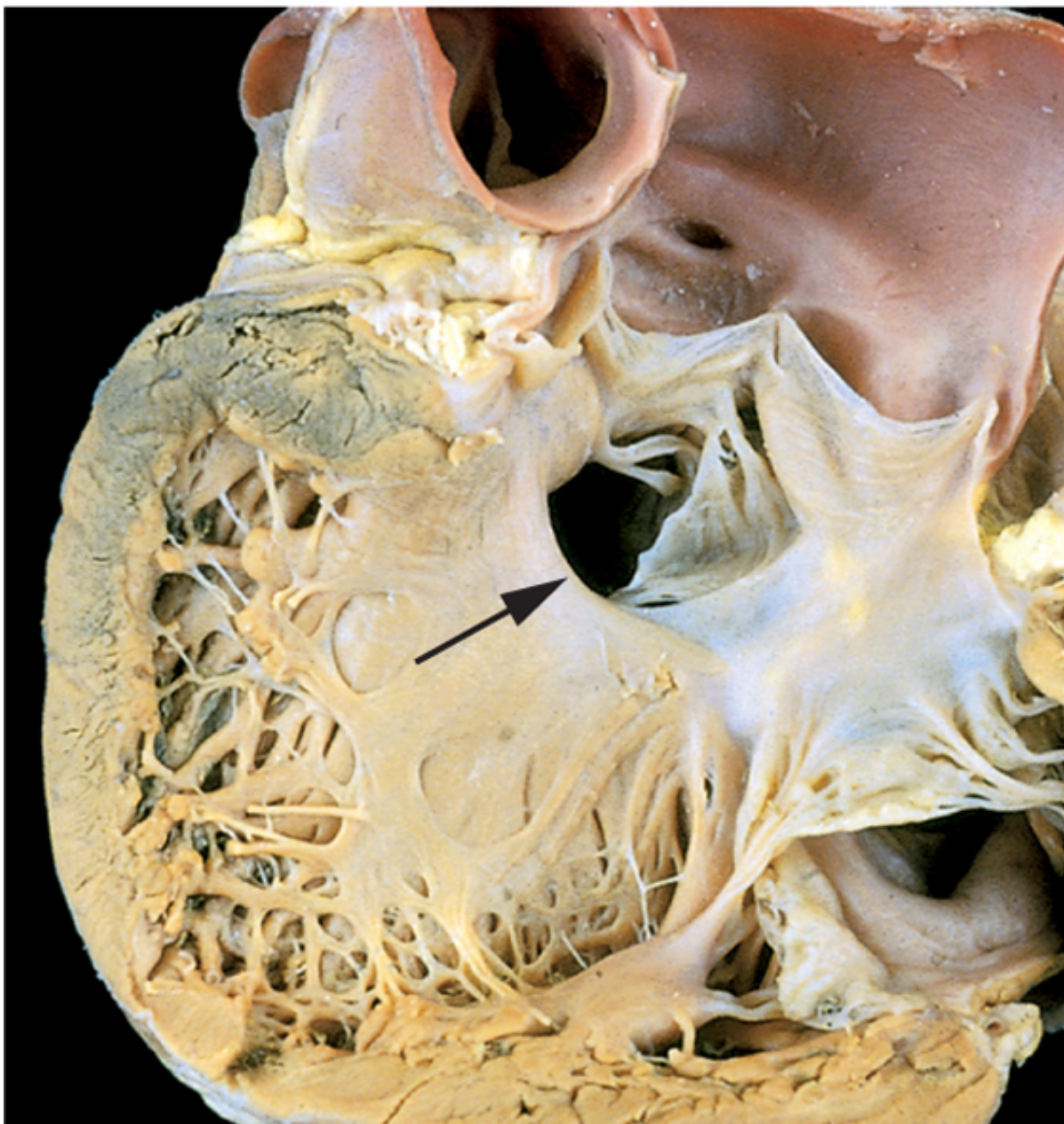
### Morphology

The size and location of VSDs are variable, ranging from minute defects in the muscular portions of the septum (Fig. 11-3) to large defects involving virtually the entire septum. With a significant left-to-right shunt, the right ventricle is hypertrophied and often dilated, and the pulmonary artery is increased because of the increased volume ejected by the right ventricle. The changes typical of pulmonary hypertension are common (Chapter 13).

#### *Clinical Features*

Small VSDs may be asymptomatic, and those in the muscular portion of the septum may close spontaneously. Larger defects, however, cause a severe left-to-right shunt, often complicated by pulmonary hypertension, with resultant reversal of the shunt and cyanosis, occurs earlier and more frequently than in those with ASDs; hence, early surgical correction is indicated for such lesions. Small- or medium-sized VSDs are also prone to superimposed infective endocarditis.

#### ***Patent Ductus Arteriosus***





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Figure 11-3 Gross photograph of a ventricular septal defect (membranous type, arrow). (Courtesy of Dr. William D

During intrauterine life, the ductus arteriosus permits blood flow from the pulmonary artery to the aorta, bypassing the unoxygenated lungs. Shortly after birth, however, the ductus constricts; this occurs in response to decreased pulmonary vascular resistance, and declining local levels of prostaglandin E<sub>2</sub>. In healthy infants, the ductus is nonpatent within 1 to 2 days after birth; complete, structural obliteration occurs within the first few weeks, forming the *ligamentum arteriosum*. Ductal closure is often delayed (or even absent) in infants with hypoxia (respiratory distress syndrome). PDAs account for about 7% of cases of congenital heart lesions (Table 11-1 and Fig. 11-1C). The remaining occur with other congenital defects, most commonly VSDs.

### Morphology

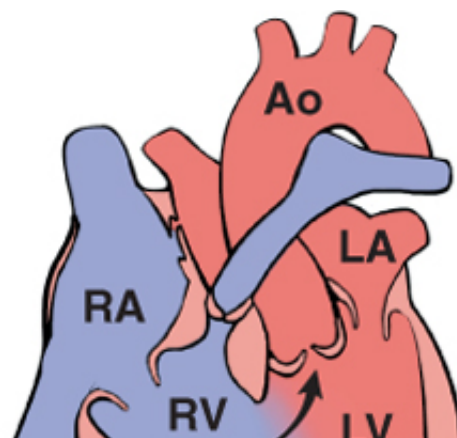
The ductus arteriosus arises from the left pulmonary artery and joins the aorta just distal to the left subclavian artery. In PDAs some of the oxygenated blood flowing out from the aorta is shunted back to the lungs (Fig. 11-1C). Because of the resultant volume overload, the proximal aorta, left atrium, and ventricle can become dilated. With the development of pulmonary hypertension and atherosclerosis of the main pulmonary arteries and proliferative changes in more distal branches, the ductus is often seen, followed by right heart hypertrophy and dilation.

### Clinical Features

PDAs are high-pressure left-to-right shunts, audible as harsh "machinery-like" murmurs. A small PDA, although larger bore defects can eventually lead to the Eisenmenger syndrome with cyanosis and predisposes affected individuals to infective endocarditis. While there is general agreement that it is not feasible, preservation of ductal patency (by administering prostaglandin E) may be critical in certain cases of congenital heart disease wherein the PDA is the only means to provide systemic or pulmonary blood flow (e.g., transposition of the large arteries). Ironically, then, the ductus can be either life threatening or lifesaving.

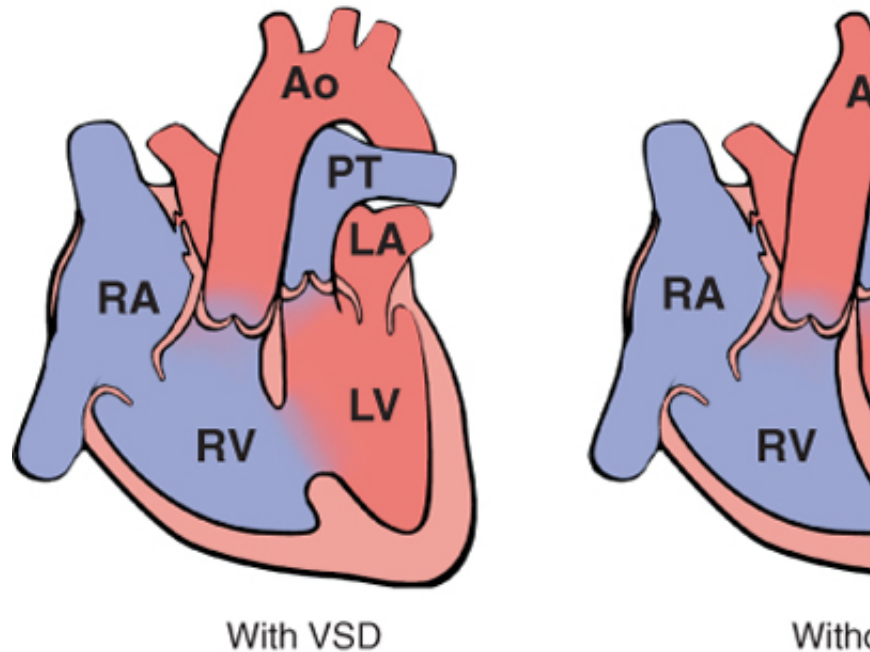
### Right-to-Left Shunts

Cardiac malformations associated with right-to-left shunts are distinguished by *cyanosis at or near birth*. In these conditions, poorly oxygenated blood from the right side of the heart is introduced directly into the arterial circulation. Conditions associated with cyanotic congenital heart disease are *tetralogy of Fallot* and *transposition of the large arteries*. Clinical findings associated with severe, long-standing cyanosis include clubbing of the fingertips and *polycythemia*. In addition, right-to-left shunts permit venous emboli to bypass the lungs and enter the systemic circulation (*paradoxical embolism*).





A Classic Tetralogy of Fallot



B Complete Transposition

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Figure 11-4 Schematic diagram of the most important right-to-left shunts (cyanotic congenital heart disease). **A**, Tetralogy of Fallot. **B**, Transposition of the great vessels with and without VSD. (Ao, aorta; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle.) (Courtesy of Dr. William D. Edwards, Mayo Clinic, Rochester,

### Tetralogy of Fallot

Accounting for about 5% of all congenital cardiac malformations, *tetralogy of Fallot is the most common cyanotic congenital heart disease* (Table 11-1). The four features of the tetralogy are (1) VSD, (2) obstruction to the right ventricular outflow tract (pulmonary stenosis), (3) an aorta that overrides the VSD, and (4) right ventricular hypertrophy (Fig. 11-4). All tetralogy patients can survive into adult life; the clinical severity largely depends on the degree of

#### Morphology

The heart is large and "boot shaped" in tetralogy of Fallot as a result of right ventricular hypertrophy. The proximal aorta is typically larger than normal, with a diminished pulmonary trunk. The left atrium and left ventricle are normal sized, while the right ventricular wall is markedly thickened and the right ventricle is displaced anteriorly and to the right. The VSD lies in the vicinity of the membranous portion of the interventricular septum. The aortic valve lies immediately over the VSD. The pulmonary outflow tract is narrowed by the infundibular stenosis. The pulmonic valve may be stenotic. Additional abnormalities are present in many cases, but these are actually beneficial in many respects, because they permit pulmonary blood flow.

#### Clinical Features



The hemodynamic consequences of tetralogy of Fallot are right-to-left shunting, decreased pulmonary volumes. *The extent of shunting* (and the clinical severity) is *determined by the amount of right ventricular* pulmonary obstruction is mild, the condition resembles an isolated VSD, because the high left-to-right shunt with no cyanosis. More commonly, marked stenosis causes significant right-to-left shunt. As patients with tetralogy grow, the pulmonary orifice does not enlarge, despite an overall increase in degree of stenosis typically worsens with time resulting in increasing cyanosis. The lungs are protected from pulmonary stenosis, so that pulmonary hypertension does not develop. As with any cyanotic heart disease, with attendant hyperviscosity, and hypertrophic osteoarthropathy; the right-to-left shunting also includes systemic emboli, and brain abscesses. Surgical correction of this defect is now possible in most infants.

### **Transposition of the Great Arteries**

Transposition of the great arteries (TGA) is a discordant connection of the ventricles to their respective vessels. It is an abnormal formation of the truncal and aortopulmonary septa, so that the aorta arises from the right ventricle and the pulmonary trunk emanates from the left ventricle (Fig. 11-4B). The atrium-to-ventricle connections, however, are normal, joining right atrium to right ventricle and left atrium to left ventricle.

The functional outcome is separation of the systemic and pulmonary circulations, a condition incompatible with life unless there exists for adequate mixing of blood and delivery of oxygenated blood to the aorta. Patients with TGA have a relatively stable shunt. However, those individuals with only a patent foramen ovale or PDA (~65%) survive and often require surgical intervention within the first few days of life.

### **Morphology**

TGA has many variants, but a detailed review of them should really be left to the cardiologist. The fundamental lesion is the abnormal origin of the pulmonary trunk and aortic root. VSD, ASD, and PDA are seen in patients surviving beyond the neonatal period. The right ventricle becomes prominent because this chamber functions as the systemic ventricle. The left ventricle becomes somewhat atrophic, since it only has to support the low-resistance pulmonary circulation.

### **Clinical Features**

The predominant manifestation of TGA is early cyanosis. The outlook for neonates with TGA depends on the magnitude of the tissue hypoxia, and the ability of the right ventricle to maintain systemic pressure. Medications used to maintain patency of the ductus arteriosus, and maneuvers such as atrial septostomy are used to improve arterial oxygen saturation. Even with stable shunting, most uncorrected TGA patients still die within the first few days of life. Affected individuals usually undergo corrective surgery (switching the great arteries) within weeks of birth.

### **Obstructive Lesions**

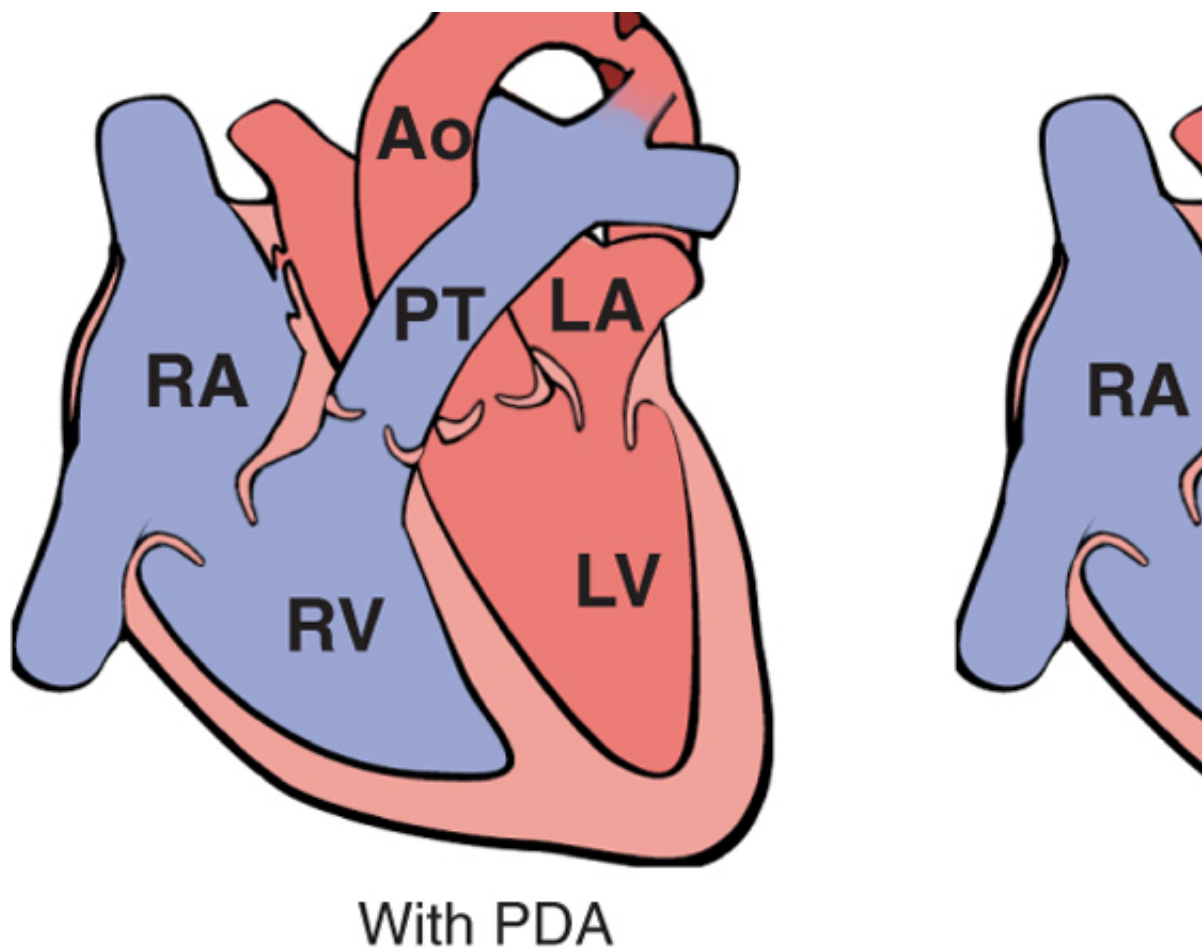
Congenital obstruction to blood flow can occur at the level of the heart valves or within a great vessel or chamber, as with subpulmonic stenosis in tetralogy of Fallot. Relatively common examples of congenital obstruction include pulmonary stenosis, aortic valve stenosis or atresia, and coarctation of the aorta.

### **Aortic Coarctation**

Coarctation (narrowing, or constriction) of the aorta is a relatively common structural anomaly (Fig. 11-5) and is the most common form of obstructive congenital heart disease. Males are affected twice as often as females, although females can have aortic coarctation. Two classic forms have been described (Fig. 11-5): an "infantile" form with a PDA, and an "adult" form in which there is a discrete ridgelike infolding of the aorta, just opposite the subclavian arch vessels. Coarctation of the aorta may occur as a solitary defect, but in more than 50% of cases it is associated with aortic valve. Congenital aortic stenosis, ASD, VSD, or mitral regurgitation may also occur. In some cases, coarctation coexists with other congenital heart defects.







## Coarctation of Aorta

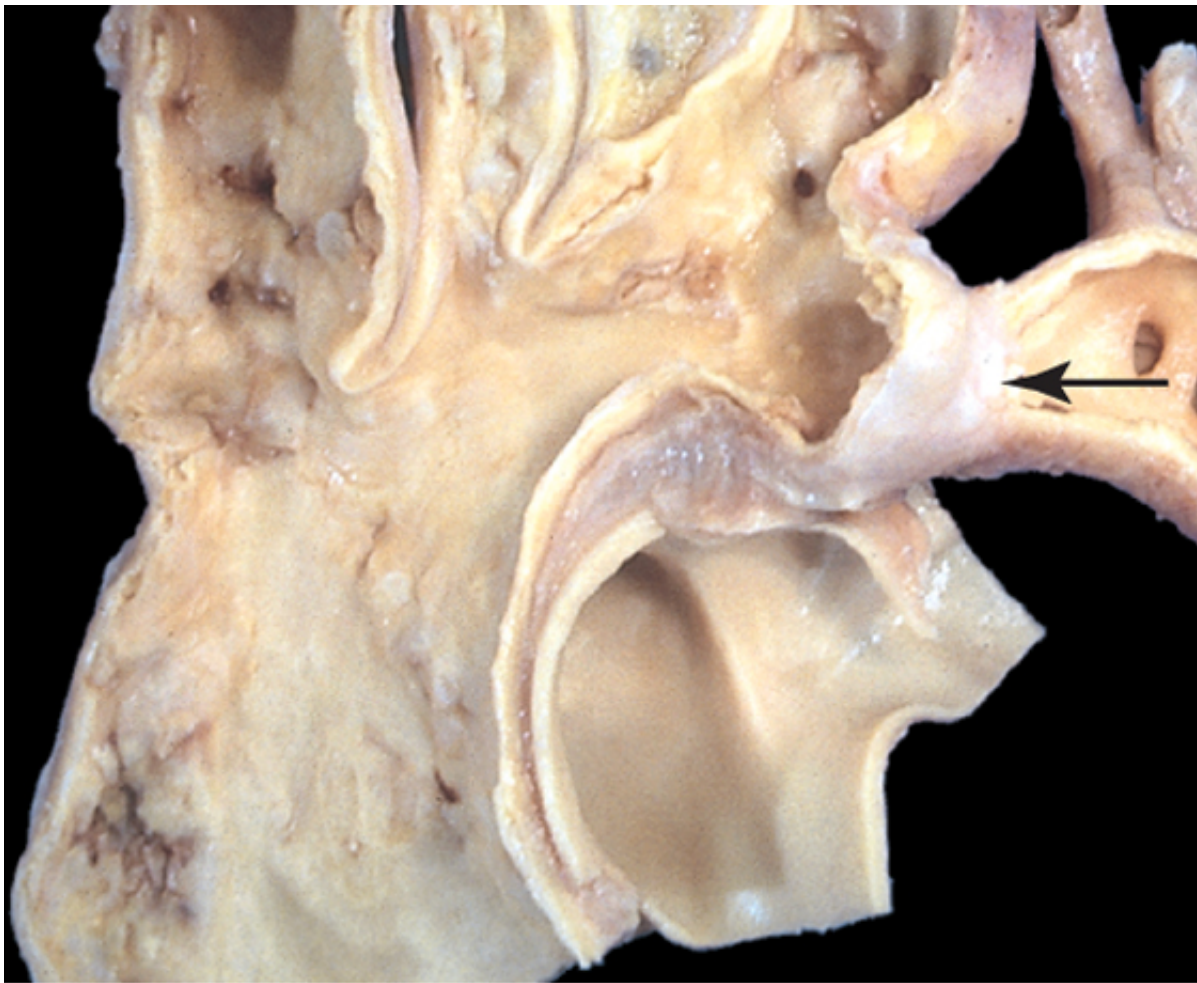
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 Figure 11-5 Coarctation of the aorta with and without a patent ductus arteriosus (PDA). Ao, aorta; LA, left atrium; PT, pulmonary trunk; RV, right ventricle. (Courtesy of Dr. William D. Edwards, Mayo Clinic, Rochester, MN)

### Morphology

Preductal ("infantile") coarctation is characterized by tubular narrowing of the aortic subclavian artery and the ductus arteriosus. The ductus arteriosus is usually patent, and blood delivered to the distal aorta. Because the right side of the heart must perfuse the body through the narrowing, the right ventricle is typically hypertrophied and dilated; the pulmonary trunk accommodates the increased blood flow.

In the more common postductal ("adult") coarctation, the aorta is sharply constricted just distal to the ligamentum arteriosum (Fig. 11-6). The constricted segment is made of dense, fibrous, and elastic fibers that are continuous with the aortic media and are lined by a thickened intima. The ductus arteriosus is closed. Proximal to the coarct, the aortic arch and its branch vessels are dilated. In older patients, often atherosclerotic. The left ventricle is hypertrophied.





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Figure 11-6 Coarctation of the aorta, postductal type. The area of coarctation is visible here as a segmental narrowing. This type of coarctation usually presents later in life than do preductal coarctations. Note the dilated ascending aorta and major branch vessels to the upper extremities. The blood flow to the lower extremities reaches the lower extremities via dilated, tortuous collateral channels. (Courtesy of Dr. Sid Murphree, Department of Pathology, University of Texas Medical School, Dallas, Texas.)

### *Clinical Features*

Clinical manifestations depend almost entirely on the severity of the narrowing and the patency of the collateral circulation.

*Preductal coarctation of the aorta with a PDA* usually leads to manifestations early in life, hence the term preductal coarctation; indeed, it may cause signs and symptoms immediately after birth. In such cases, the blood flow to the lower extremities through the ductus arteriosus produces cyanosis localized to the lower half of the body. Femoral pulses are weak or absent, while those of the upper extremities are strong. Many such infants do not survive the neonatal period without intervention.

*Postductal coarctation of the aorta without a PDA* is usually asymptomatic, and the disease may go undetected until adulthood. Typically, there is upper extremity hypertension, due to poor perfusion of the kidneys, but weak pulses in the lower extremities. Claudication and coldness of the lower extremities result from arterial insufficiency. Collateral circulation "around" the coarctation involving markedly enlarged intercostal and internal thoracic arteries leads to radiographically visible "notching" of the ribs.

### **SUMMARY** **Congenital Heart Disease**

Congenital heart diseases consist of defects of cardiac chambers or the arteries and veins.

congenital heart diseases consist of defects of cardiac chambers or the great result in shunting of blood between the right and left circulation or cause out right shunts are most common and typically involve ASDs, VSDs, or a PDA. chronic right-sided pressure and volume overload that eventually causes pu reversal of flow and right-to-left shunts with cyanosis (Eisenmenger syndror typically caused by tetralogy of Fallot or transposition of great vessels. These from the outset and are associated with polycythemia, hypertrophic osteoar emboli. Obstructive lesions include aortic coarctation; the clinical severity of degree of stenosis and the patency of the ductus arteriosus.



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## ISCHEMIC HEART DISEASE (IHD)

IHD is a generic designation for a group of related syndromes resulting from myocardial *ischemia* (inadequate blood supply (perfusion) and myocardial oxygen demand. Although ischemia can result from increased blood pressure (hypertension), or diminished oxygen-carrying capacity (e.g., anemia, carbon monoxide poisoning), or a reduction in coronary blood flow caused by obstructive atherosclerotic disease ([Chapter 10](#)), the most common cause is coronary artery disease (CAD). Despite dramatic improvement over the past 3 to 4 decades, IHD remains the leading cause of death in the United States and other industrialized nations.

The clinical manifestations of IHD are a direct consequence of insufficient blood supply to the heart muscle. The syndromes of IHD:

*Angina pectoris* (literally *chest pain*), wherein the ischemia causes pain but is insufficient to cause permanent damage. Angina may be *stable* (occurring reliably after certain levels of exertion), may be *variant* (*Prinzmetal angina*), or may be *unstable* (occurring with progressively less exertion or even at rest). Unstable angina wherein the severity or duration of ischemia is enough to cause cardiac muscle death. *Chronic heart failure* (heart failure) following MI. *Sudden cardiac death (SCD)*, can result from a fatal arrhythmia during ischemia. As discussed later, there are other causes of SCD as well.

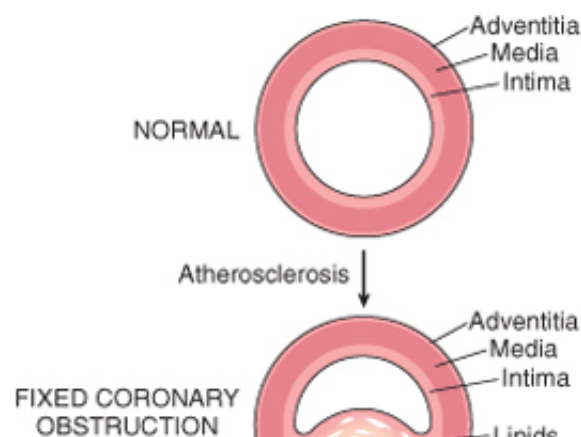
These syndromes are all relatively late manifestations of coronary atherosclerosis that begins early in life. As the vascular occlusions reach a critical stage. The term *acute coronary syndrome* is applied to three conditions: unstable angina, acute MI, and SCD.

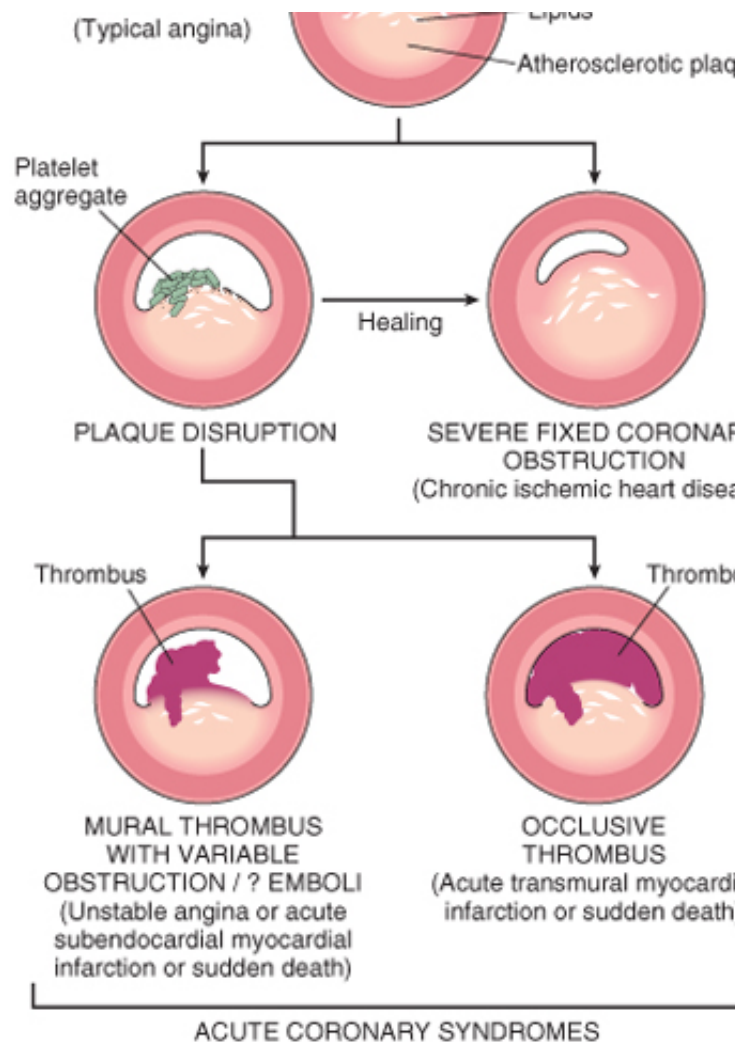
### *Epidemiology*

Nearly 500,000 Americans die of IHD annually; nevertheless, this represents a spectacular improvement. In 1963, the overall death rate from IHD has fallen in the United States by approximately 50%. This is due to the recognition of cardiac risk factors (that is, risk factors leading to atherosclerotic disease; [Chapter 10](#)): smoking, treating hypertension and diabetes, and lowering cholesterol. To a lesser extent, *diagnostic and therapeutic advances*; these include coronary angiography, [aspirin](#)<sup>®</sup> prophylaxis, newer medications like statins, cardiac care units, angioplasty and endovascular stents, thrombolysis for MI, and coronary artery bypass grafting. Progress in the 21st century will be particularly challenging in view of the predicted increased long

### *Pathogenesis*

In most cases IHD occurs because of inadequate coronary perfusion relative to myocardial demand. This is usually due to pre-existing ("fixed") atherosclerotic occlusion of coronary arteries and new superimposed thromb





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Figure 11-7 Sequential progression of coronary artery lesion morphology, beginning with stable chronic plaque, resulting in various acute coronary syndromes. (Modified and redrawn from Schoen FJ: Interventional and Surgical Cardiovascular Principles. Philadelphia, WB Saunders, 1989, p 63.)

A lesion obstructing 70% to 75% or more of a vessel lumen—so-called critical stenosis—generally causes symptoms only in the setting of increased demand (Fig. 11-7); a fixed 90% stenosis can lead to inadequate coronary flow. Importantly, if a coronary artery develops atherosclerotic occlusion at a sufficiently slow rate, it may recruit collateral flow from other major epicardial vessels; such *collateral perfusion* can then protect against MI even after complete occlusion. Unfortunately, acute coronary occlusions cannot spontaneously recruit collateral flow and lead to MI.

Although only a single major coronary epicardial artery may be affected by atherosclerotic narrowing, the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)—can be concurrently involved. Lesions are located anywhere but tend to predominate within the first several centimeters of the LAD and LCX. Sometimes, secondary branches are also involved (i.e., diagonal branches of the LAD, obtuse marginal branches of the RCA). It should be emphasized that symptom onset depends not only on the extent of atherosclerotic disease but also critically on dynamic changes in coronary plaque morphology (see below).

#### Role of Acute Plaque Change

In most patients, unstable angina, infarction, and many cases of SCD all occur because of abrupt changes in plaque morphology (Fig. 11-7), hence the term acute coronary syndrome. The initiating event is typically disruption of the plaque.

*Rupture, fissuring, or ulceration of plaques exposing highly thrombogenic plaque constituents to the bloodstream*



basement membrane. Hemorrhage into the core of plaques with expansion of plaque volume leads to thrombotic occlusion.

The events that trigger the abrupt plaque changes are complex. They may be intrinsic to the structure of the plaque. Basically, rupture reflects the inability of a plaque to withstand mechanical stresses.

Plaques that contain a large atheromatous core or those in which the overlying fibrous caps are thin and fragile are therefore denoted as "vulnerable." Fissures frequently occur at the junction of the fibrous cap and the underlying atheromatous core, a location at which the mechanical stresses are highest and the fibrous cap is thinnest. The balance of collagen synthesis and degradation determines its mechanical strength. Collagen is produced by smooth muscle cells and degraded by the action of metalloproteinases elaborated by macrophages. Consequently, a paucity of smooth muscle cells or an increase in inflammatory cell activity in a plaque may increase its vulnerability. Interestingly, statins (inhibitors of HMG Co-A reductase, a key enzyme in the synthesis of cholesterol) reduce the clinical events associated with IHD by their lipid-lowering effect, as well as by reducing plaque inflammation.

Influences extrinsic to the plaque are also important. Adrenergic stimulation can elevate physical stress, such as hypertension or local vasospasm. Indeed, the adrenergic stimulation associated with awakening is associated with a higher incidence (between 6 AM and 12 noon) of acute MIs. Intense emotional stress can also contribute to plaque rupture.

Such acute changes often develop in plaques not initially critically stenotic or even symptomatic by themselves. Symptoms typically occur with fixed lesions that cause greater than 70% to 75% occlusion. Pathologic studies of ruptured plaques are  $\leq 50\%$  stenotic before plaque rupture, and 85% have initial stenosis that is  $\leq 50\%$ . Thus, a rather large number of now asymptomatic adults in the industrial world have a significant burden of atherosclerosis that may lead to a coronary event. Regrettably, it is presently impossible to reliably predict plaque rupture in any given individual.

Accumulating evidence also indicates that plaque disruption with ensuing platelet aggregation and thrombus formation are often clinically silent complications of atherosclerosis. Moreover, healing of subclinical plaque disruption is an important mechanism by which atherosclerotic lesions progressively enlarge.

### *Role of Inflammation*

Inflammation plays an essential role at all stages of atherosclerosis, from inception to plaque rupture. Atherosclerosis begins with the interaction of endothelial cells and circulating leukocytes, resulting in their adhesion and activation. These cells subsequently drive smooth muscle cell proliferation, with variable amounts of collagen accumulating over an atheromatous core of lipid, cholesterol, calcification, and necrotic debris. At the site of plaque rupture, an atherosclerotic plaque occurs through metalloproteinase secretion.

### *Role of Thrombus*

Thrombosis associated with a disrupted plaque is critical to the pathogenesis of acute coronary syndrome. A newly formed thrombus on a disrupted atherosclerotic plaque can wax and wane with time and lead to complete or partial occlusion; alternatively, even partial luminal occlusion by thrombus can compromise blood flow sufficiently to cause a zone of the myocardium (subendocardial infarct). Mural thrombus in a coronary artery can also erode into the lumen, adding thrombotic material, along with associated microinfarcts, can be found in the distal intramyocardium. Patients who have experienced unstable angina or sudden death. In the most serious extreme, completely obstructive thrombosis can cause a massive MI. Since blood flow is abruptly blocked by thrombosis, collateral circulation can produce potent activators of smooth muscle proliferation, which can contribute to the growth of atherosclerosis.

### *Role of Vasoconstriction*

Vasoconstriction directly compromises lumen diameter; and by increasing local mechanical shear stress, it promotes plaque disruption. Vasoconstriction in atherosclerotic plaques can be stimulated by (1) circulating adrenergic hormones, (2) an imbalance between endothelial cell relaxing factors (e.g., nitric oxide<sub>Rx</sub>) versus constrictor factors (Chapter 10), and (4) mediators released from perivascular inflammatory cells.

### *Other Pathologic Processes*

Rarely, processes other than atherosclerosis and superimposed thrombi can compromise coronary arteries (e.g., valve vegetations, coronary vasculitis, and systemic hypotension. Myocardial hypertrophy (see below) can also increase myocardial demand beyond what even relatively normal coronary arteries can supply.

## Angina Pectoris

Angina pectoris is intermittent chest pain caused by transient, reversible myocardial ischemia. The

*Typical or stable angina* is episodic chest pain associated with exertion or some other form of stress (e.g., tachycardia or hypertension due to fever, anxiety, fear). The pain is classically described as a substernal sensation, which can radiate down the left arm or to the left jaw (*referred pain*). It is associated with a fixed atherosclerotic narrowing ( $\geq 75\%$ ) of one or more coronary arteries. Myocardial oxygen supply may be sufficient under basal conditions but cannot be adequate during periods of increased demand. The pain is usually relieved by rest (reducing demand) or by administering a vasodilator. Nitroglycerin also increases blood supply to the myocardium by direct coronary vasodilation. Although such spasms typically occur on completely normal vessels can be affected. The etiology is not clear, but Prinzmetal angina is characterized by increasing frequency of pain, precipitated by progressively less exertion; it is longer lasting than stable angina. As discussed above, unstable angina is associated with partial thrombosis, distal embolization of the thrombus, and/or vasospasm. Unstable angina is potentially irreversible ischemia (due to complete luminal occlusion by thrombus) and is the *precursor of myocardial infarction*.

## Myocardial Infarction

MI, popularly called *heart attack*, is *necrosis of heart muscle resulting from ischemia*. Roughly 1.5 million people die from MI every year; of these, one-third die before they can reach the hospital. The major underlying cause of MI is atherosclerosis. The frequency of MIs rises progressively with increasing age and presence of other risk factors such as hypertension and diabetes discussed in Chapter 10. Approximately 10% of MIs occur in people younger than 40 years of age. Blacks and whites are equally affected. Men are at significantly greater risk than women. In general, women are remarkably protected against MI during the premenopausal period, and the decline in estrogen production is associated with exacerbation of coronary atherosclerosis.

### Pathogenesis

Although any form of coronary artery occlusion can cause acute MI, angiographic studies demonstrate that the most common cause is *coronary artery thrombosis*. In most cases, disruption of an atherosclerotic plaque results in the formation of a thrombus. Platelet aggregation can contribute but are infrequently the sole cause of an occlusion. Sometimes, in the innermost (subendocardial) myocardium, thrombi may be absent. In these cases, severe diffuse coronary artery disease, and a prolonged period of increased demand (e.g., due to tachycardia) can cause necrosis of myocytes most distal to the epicardial vessels.

### Coronary Artery Occlusion

In a *typical MI*, the following sequence of events transpires:

There is a sudden disruption of an atheromatous plaque—for example, intraplaque hemorrhage, fissuring—exposing subendothelial collagen and necrotic plaque contents. Platelets adhere, release potent secondary aggregators including thromboxane  $A_2$ , adenosine diphosphate (ADP), and serotonin. These mediators activate the intrinsic pathway of platelet aggregation and mediator release. Other mediators activate the extrinsic pathway. Within minutes the thrombus can evolve to completely occlude the coronary lumen.

The evidence for this series of events derives from (1) autopsy studies of patients dying with acute MI, (2) the high frequency of thrombotic occlusion early after MI, (3) the high success rate of

angioplasty, and (4) the demonstration of residual disrupted atherosclerotic lesions by angiography. Coronary angiography performed within 4 hours of the onset of MI shows a thrombosed coronary artery; when angiography is delayed until 12 to 24 hours after onset of symptoms, occlusions are observed. Thus, at least some occlusions seem to clear spontaneously as a result of lysis of the thrombus. However, if no intervention is performed, any residual thrombus is likely to be incorporated into the growing atherosclerotic plaque.

### Myocardial Response to Ischemia

Coronary artery obstruction blocks the myocardial blood supply, leading to profound functional, biochemical, and structural consequences. Within seconds of vascular obstruction, cardiac myocyte aerobic glycolysis ceases, and adenosine triphosphate (ATP) is depleted, leading to accumulation of potentially noxious breakdown products (e.g., lactic acid). The consequence is a striking loss of contractility, occurring within a minute or so of the onset of ischemia. Myofibrillar relaxation, glycogen depletion, and cell and mitochondrial swelling also become rapid. These changes are potentially reversible, and myocardial cell death is not immediate (Chapter 1). Only several minutes of severe ischemia causes irreversible injury and myocyte death; the predominant pattern is coagulation necrosis. If reperfusion occurs, microvasculature injury ensues.

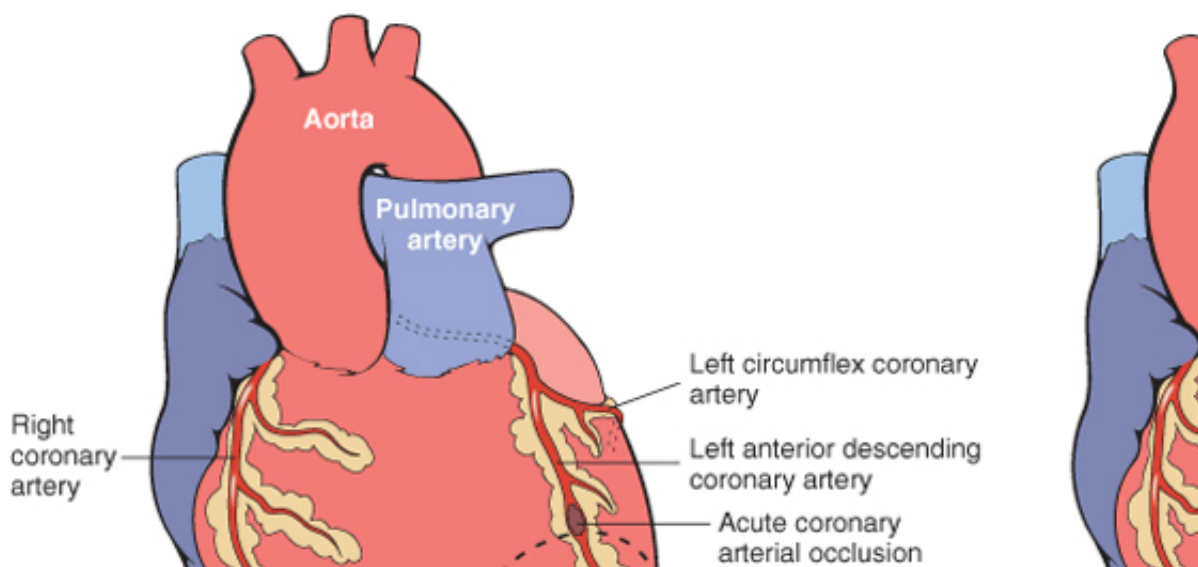
If myocardial blood flow is restored anywhere along this timeline (*reperfusion*), cell viability may be improved. This is the basis for early clinical detection of acute MI, and prompt intervention by angioplasty or thrombolysis, to restore blood flow. Ischemic but still viable myocardium can be salvaged by early reperfusion. However, as discussed in Chapter 1, reperfusion can have untoward effects.

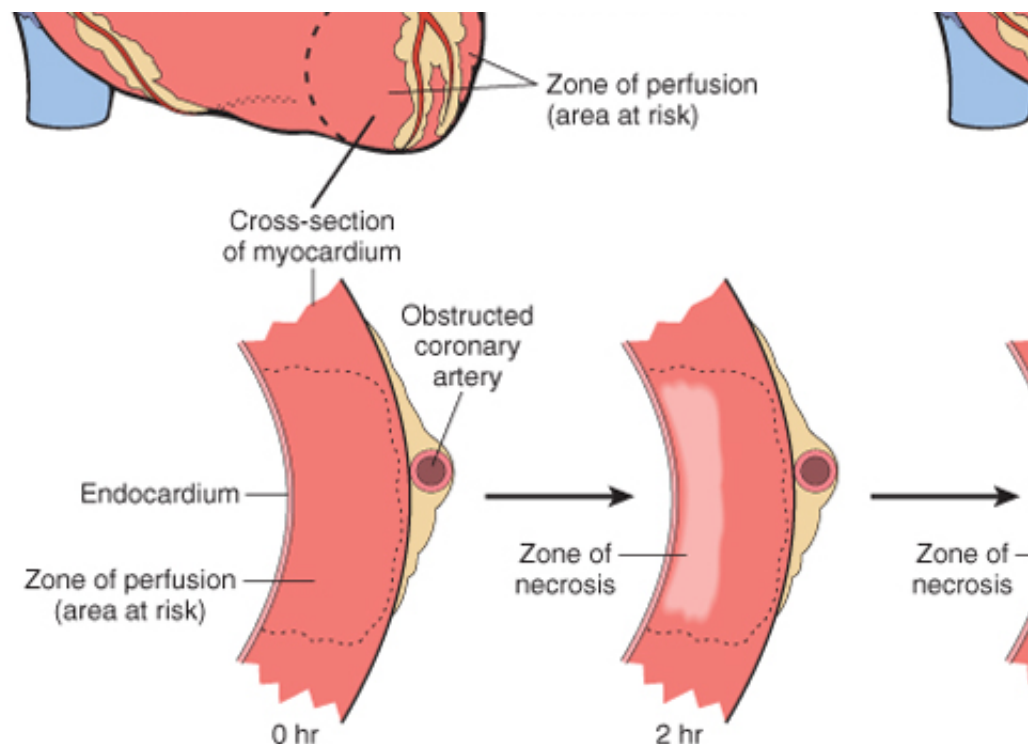
Myocardial ischemia also contributes to arrhythmias, probably by causing *electrical instability* (irritability). Although massive myocardial damage can clearly cause a fatal mechanical failure, SCD in the setting of MI is usually (80% to 90% of cases) due to ventricular fibrillation caused by myocardial irritability.

Irreversible injury of ischemic myocytes first occurs in the subendocardial zone (Fig. 11-8). Not only is the subendocardium furthest from the blood delivered by the epicardial vessels, the relatively higher intramural pressures there further compromise blood flow. With prolonged ischemia, a wavefront of cell death moves through the myocardium to involve progressively more of the subendocardial zone, so that an infarct usually reaches its full size within 3 to 6 hours. Any intervention to restore blood flow must occur before the final extent of necrosis is established.

The final location, size, and specific morphologic features of an acute MI depend on:

- Location, severity, and rate of development of the coronary occlusion
- Size of the vascular bed supplied by the occluded vessel
- Duration of the occlusion
- Metabolic demands of the myocardium (affected, e.g., by heart rate, contractility, and temperature)
- Availability of collateral supply.





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Figure 11-8 Progression of myocardial necrosis after coronary artery occlusion. Necrosis begins in a small zone of in the center of the ischemic zone. This entire region of myocardium depends on the occluded vessel for perfusion zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated obstruction to blood flow is necrosis of the muscle that was dependent on perfusion from the coronary artery obstru

### Morphology

Nearly all transmural infarcts (defined as involving  $\geq 50\%$  of the myocardial wall this portion of the left ventricle and/or ventricular septum. Roughly 15% to 30% of MIs a posteroseptal wall also extend into the adjacent right ventricular wall. Isolated right however, occur in only 1% to 3% of cases. Even in transmural infarcts, a narrow rim subendocardial myocardium is preserved by diffusion of oxygen and nutrients from

In 90% of the population the posterior descending artery is supplied by the right coronary artery (said to have right dominant coronary artery), the following distribution c

Left anterior descending artery (40% to 50%): infarct involves anterior left ventricle and apex circumferentially. Right coronary artery (30% to 40%): infarct involves posterior septum, and right ventricular free wall in some cases. Left circumflex infarct involves lateral left ventricle except the apex.

Other coronary occlusions are occasionally encountered. These include the left main coronary artery and its secondary branches, such as the diagonal branches of the LAD artery or marginal artery. In contrast, significant atherosclerosis or thrombosis of penetrating intramyocardial coronary arteries rarely occur. Severe coronary occlusion without associated myocardial necrosis is the prior formation of protective collateral connections.

The gross and microscopic appearance of an MI depends on the interval of time since its onset (Table 11-2). Areas of damage undergo a progressive and highly characteristic series of changes. Despite recent excitement about potential myocardial repopulation by resident stem cells, myocardial necrosis proceeds invariably to scar formation without any significant

Early recognition of acute MIs can be challenging, particularly when death occurs very soon after symptom onset. **MIs less than 12 hours old are usually not grossly apparent.** Infarcts less than 3 hours old can be visualized by exposing heart slices to vital stains (e.g., triphenyltetrazolium chloride, a substrate for lactate dehydrogenase in viable heart). Because dehydrogenases are released during ischemic necrosis (they leak through damaged cell membranes and can actually be detected in MI in peripheral blood samples; [Chapter 1](#)), an infarcted area is revealed as an area of discoloration. As scars appear white and glistening; [Fig. 11-9](#)). By **12 to 24 hours after MI, an infarct is grossly identified by a reddish blue discoloration** caused by stagnant, trapped blood. Thereafter, an infarct becomes more sharply delineated as a yellow-tan, softened area. Older infarcts become rimmed by hyperemic (highly vascularized) granulation tissue. Over time, the MI evolves to a fibrous scar.

The microscopic appearance also undergoes a characteristic sequence of changes ([Fig. 11-10](#)). Typical features of **coagulative necrosis** ([Chapter 1](#)) become detectable with infarction. **"Wavy fibers"** can also be present at the edges of an infarct; these reflect buckling of noncontractile dead fibers but are considered "soft" findings of acute infarction. Ischemia can also induce myocyte vacuolization. These are large cleared intracellular spaces containing water; such myocytes are still alive but are poorly contractile.

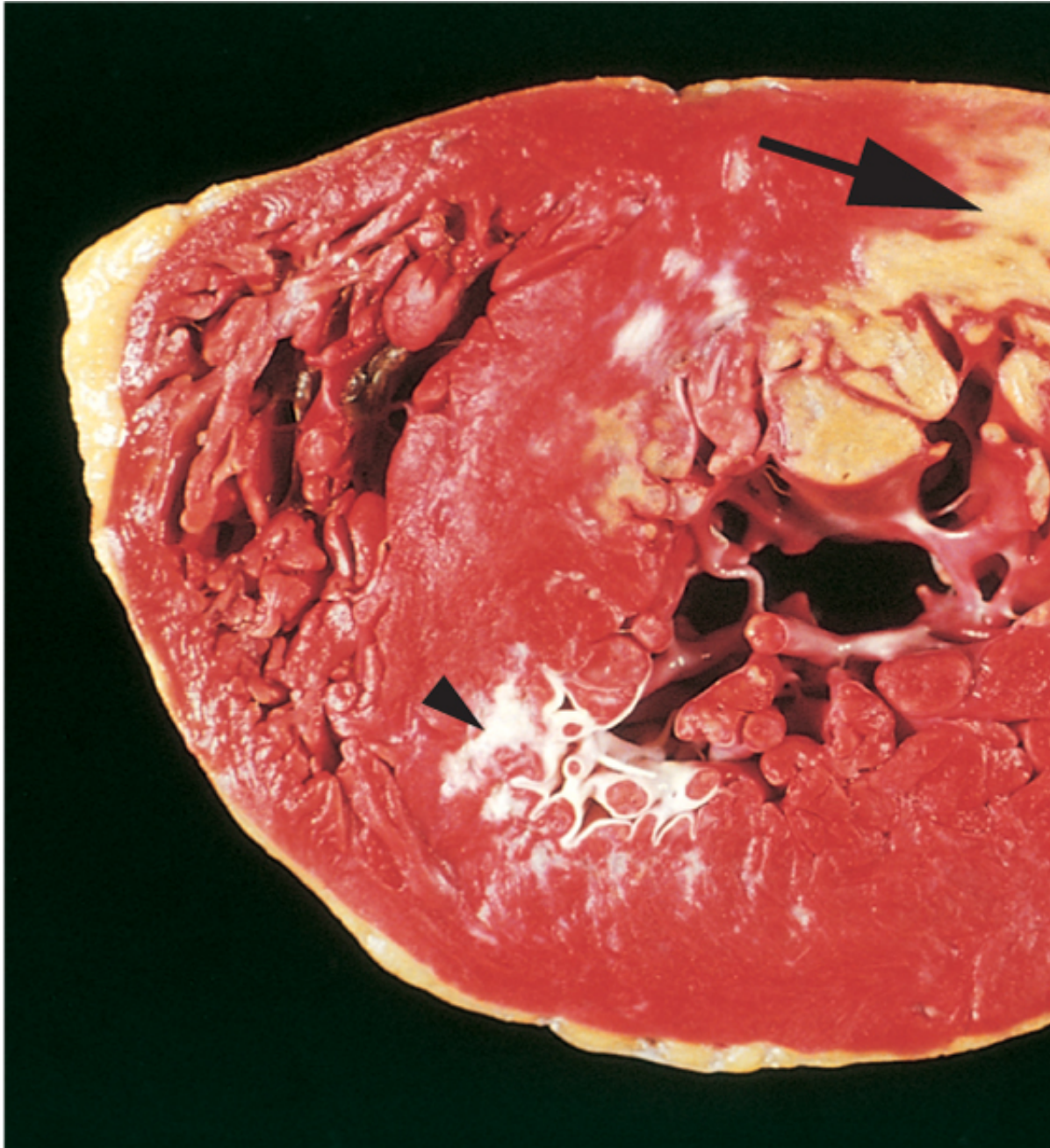
Necrotic myocardium elicits **acute inflammation** (typically most prominent 1-3 day after MI). The infarcted zone is progressively replaced by **granulation tissue** (most prominent 3-7 days after MI), which in turn forms the provisional scaffolding upon which dense **collagen** scar forms. In most instances scarring is well advanced by the end of the sixth week, but the efficacy of healing depends on the size of the original lesion. Healing requires the migration of inflammatory cells from the periphery of the infarct toward the center, and a large infarct may not heal as readily or completely. Once an MI is completely healed, it is impossible to distinguish its age (i.e., the 1-week-old and 10-year-old lesions look similar).

**Table 11-2. Evolution of Morphologic Changes in Myocardial Infarction**

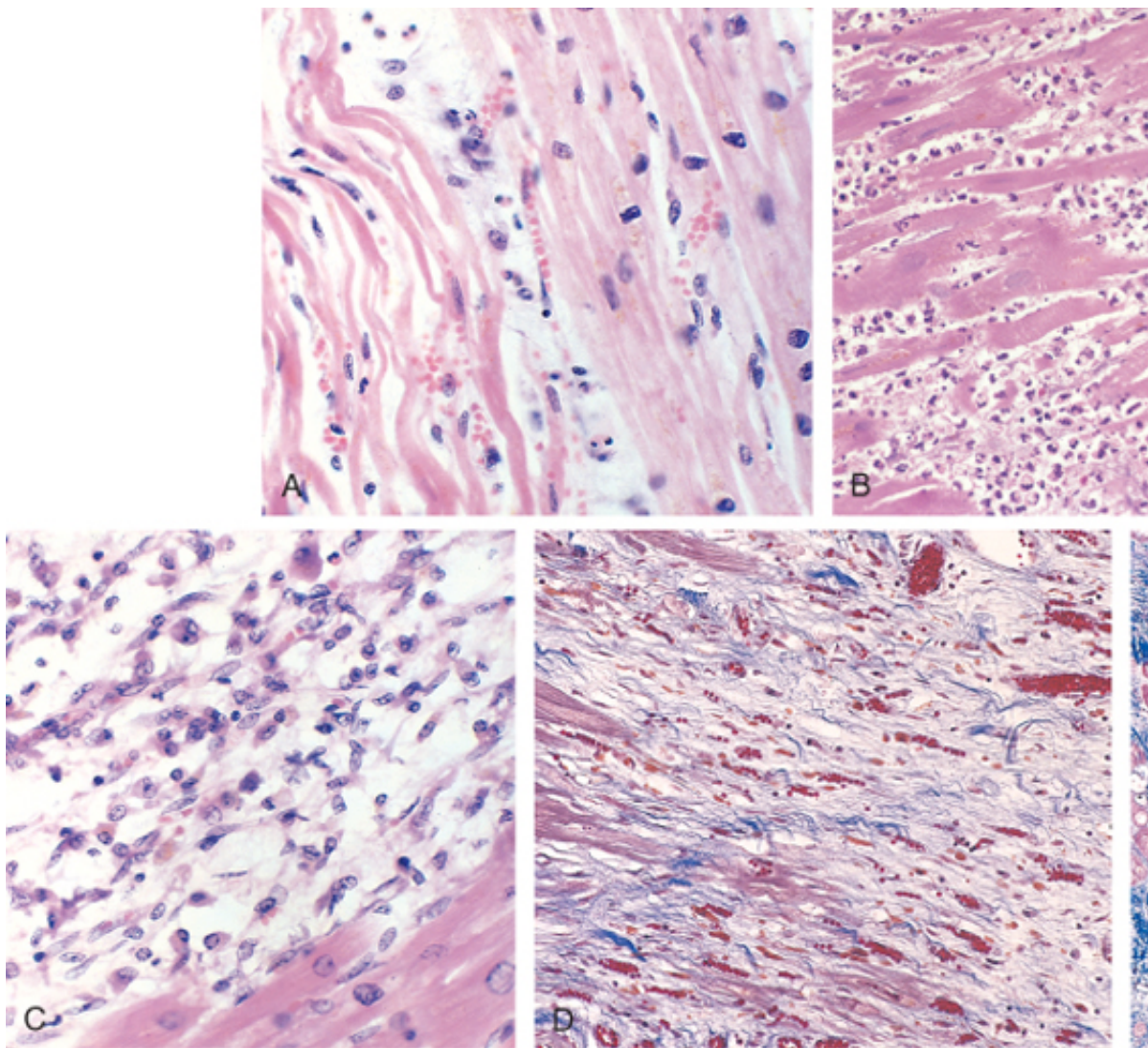
Time Gross Features		Light Microscopic Findings
<b>Reversible Injury</b>		
0-½ hr	None	None
<b>Irreversible Injury</b>		
½-4hr	None	Usually none; variable waviness of fibers at border
4-12hr	Occasionally dark mottling	Beginning coagulation necrosis; edema; hemorrhage
12-24hr	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; beginning neutrophilic infiltrate
1-3 days	Mottling with yellow-tan infarct center	Coagulation necrosis, with loss of nuclei and striations; interstitial infiltrate of neutrophils
3-7 days	Hyperemic border; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; phagocytosis of dead cells by macrophages at infarct border
7-10	Maximally yellow-tan and soft,	Well-developed phagocytosis of dead cells; early formation of



days	with depressed red-tan margins	fibrovascular granulation tissue at margins
10-14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition
2-8wk	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity
>2mo	Scarring complete	Dense collagenous scar



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 Figure 11-9 Acute myocardial infarct of the posterolateral left ventricle demonstrated by a lack of triphenyl tetrazolium staining. The staining defect is due to leakage of lactate dehydrogenase after cell death. Note the anterior scar (arrow) and the hemorrhage at the right edge of the infarct (asterisk) is due to ventricular rupture and was the acute cause of death (the posterior wall at the top).



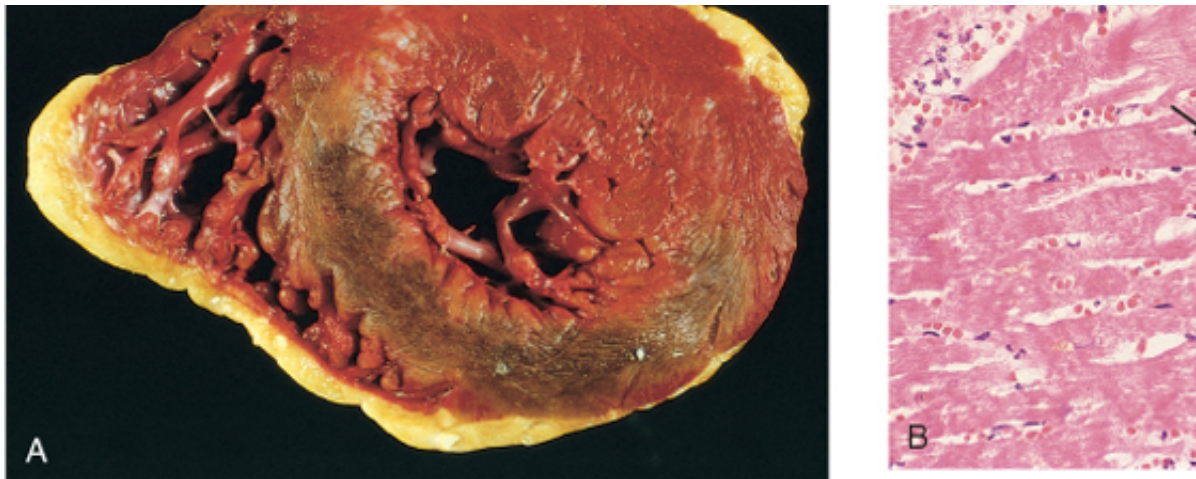
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 Figure 11-10 Microscopic features of MI and its repair. **A**, One-day-old infarct showing coagulative necrosis along fibers (at right). Widened spaces contain edema fluid and scattered neutrophils. **B**, Dense polymorphonuclear leukocyte infiltration. **C**, Nearly complete removal of necrotic myocytes by macrophage phagocytosis (7-10 days). **D**, Granulation tissue with new capillaries. **E**, Well-healed myocardial infarct with replacement of the necrotic fibers by dense collagenous scar. **A** and **E**, Masson's trichrome stain to accentuate the collagen (staining peac

#### Changes in an Infarct due to Reperfusion

The current therapeutic goal in acute MIs is to salvage the maximal amount of ischemic myocardium as quickly as possible. Such *reperfusion* is achieved by thrombolysis (dissolution of thrombus by streptokinase activator), balloon angioplasty (with or without stenting), or coronary arterial bypass graft. Unfortunately, reperfusion of the at-risk heart can improve both short- and long-term outcomes, reperfusion is not a completely innocuous entity of *reperfusion injury* that can incite *greater* local damage than might have otherwise occurred with continued blood flow. As discussed in Chapter 1, reperfusion injury is mediated in part by oxygen free radicals and infiltrating leukocytes facilitated by reperfusion. Reperfusion-induced microvascular injury causes swelling that occludes capillaries and may prevent local blood flow (called *no-reflow*).







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Figure 11-11 Consequences of myocardial ischemia followed by reperfusion. **A** and **B**, Gross and microscopic app  
**A**, Large, hemorrhagic, anterior-wall MI from patient treated with streptokinase<sup>®</sup> (triphenyl tetrazolium chloride-sta  
 Myocardial necrosis with hemorrhage and contraction bands, visible as hypereosinophilic band:

The typical appearance of ischemic and reperfused myocardium is shown in Figure 11-11A and B hemorrhage because the vasculature injured during the period of ischemia is leaky after flow is re subjected to reperfusion also show *contraction band necrosis*. Contraction bands are intensely eo hypercontracted sarcomeres. These are due to exaggerated contraction of myofibrils occurring w/ concentrations in the restored blood flow are able to cross damaged plasma membranes and driv absence of ATP to allow relaxation, the sarcomeres are stuck in this final agonal tetanic state. Thi reversibly injured cells but also alters the morphology of cells already lethally injured at the time o

It should be noted that despite timely reperfusion and salvage, ischemic (but viable) myocardium i most of this viable myocardium can ultimately recover normal function, abnormalities in cellular bi after ischemia and lead to a noncontractile state (*stunned myocardium*). Such stunning can produ failure that may require pump assistance to support the patient until cardiac function returns.

### Clinical Features

An MI is usually heralded by severe, crushing substernal chest pain or discomfort that can radiate In contrast to the pain of angina pectoris, the pain of an MI typically lasts from 20 minutes to sever by nitroglycerin<sup>®</sup> or rest. In a substantial minority of patients (10% to 15%) MIs can be entirely as particularly common in patients with underlying diabetes mellitus (with peripheral neuropathies) ar

With MIs the pulse is generally rapid and weak, and patients can be diaphoretic and nauseated p; Dyspnea is common and is caused by impaired myocardial contractility and dysfunction of the mit pulmonary congestion and edema. With massive MIs (>40% of the left ventricle) cardiogenic shoc

*Electrocardiographic abnormalities* are important markers of MIs; these include changes such as i and ST-segment abnormalities and T-wave inversion (representing abnormalities in myocardial re electrical abnormalities of the ischemic myocardium and conduction system are common, and ind accounts for the vast majority of deaths occurring before hospitalization.

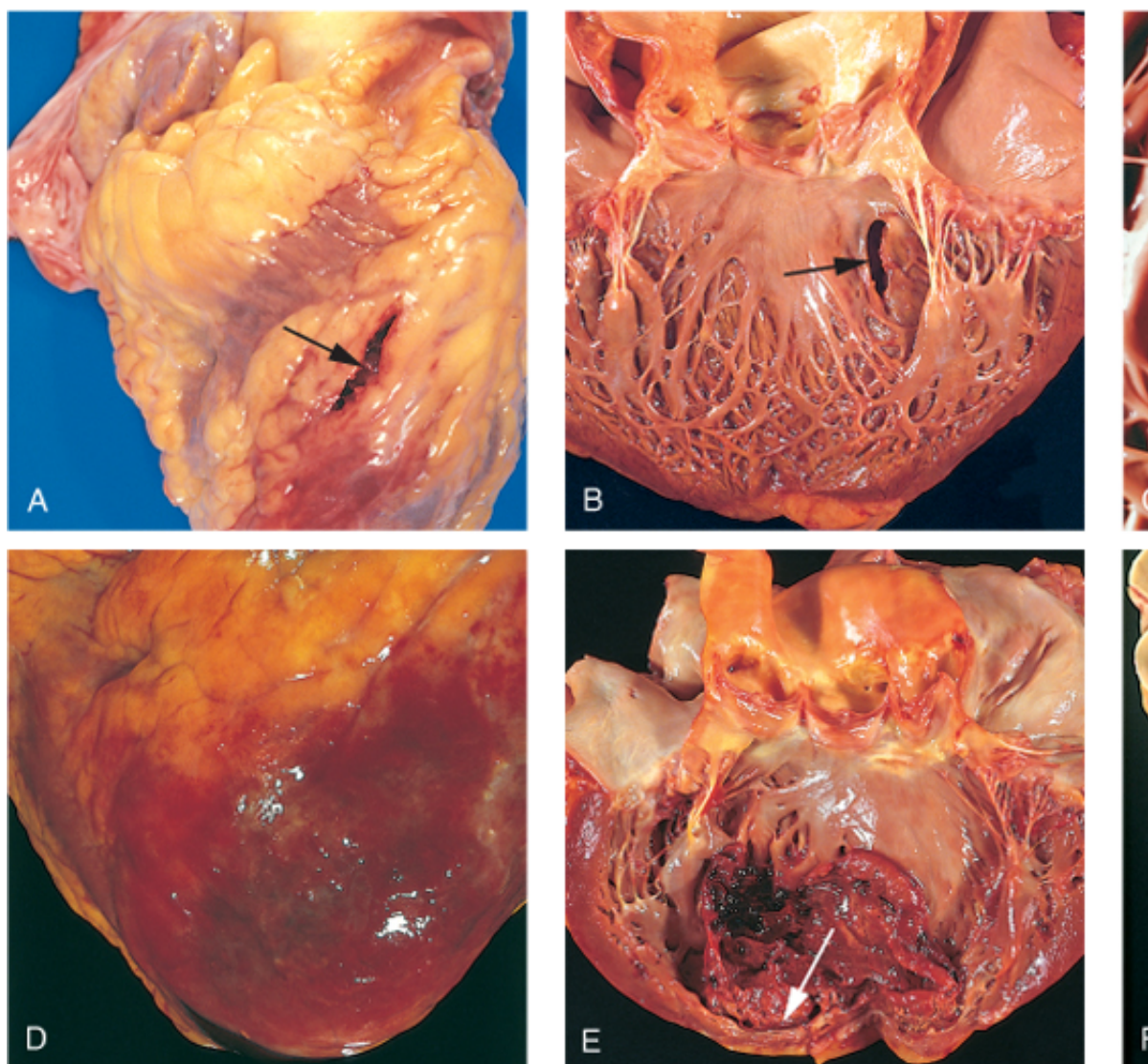
*Laboratory evaluation* of MI is based on measuring the blood levels of intracellular macromolecule through damaged cell membranes; these molecules include myoglobin, cardiac troponins T and I more specifically the myocardial-specific isoform, CK-MB), lactate dehydrogenase, and many othe specificity and sensitivity for myocardial damage.

TnI and TnT are not normally detectable in the circulation, but after acute MI both troponins becor at 48 hours; their levels remain elevated for 7 to 10 days. CK-MB is the second best marker after various forms of CK are found in brain, myocardium, and skeletal muscle, total CK activity is not a

could come from skeletal muscle injury). Thus, the CK-MB isoform-principally derived from myocardium and not skeletal muscle-is the more specific indicator of heart damage. CK-MB activity begins to rise within 4-6 hours, and returns to normal within approximately 72 hours. Although cardiac troponin and CK-MB levels rise after an MI, persistence of elevated troponin levels for approximately 10 days allows the diagnosis of a heart attack. With reperfusion, both troponin and CK-MB peaks occur earlier as a result of reperfusion injury.

### *Consequences and Complications of MI*

Extraordinary progress has been made in patient outcomes subsequent to acute MI; since the 1970s, the mortality rate has declined from approximately 30% to an overall rate of between 10% and 13% today (and to ~7% with reperfusion therapy). Unfortunately, half of the deaths associated with acute MI occur in individual patients generally die within 1 hour of symptom onset-usually as a result of arrhythmias. The variables associated with poor outcome include advanced age, female gender, diabetes mellitus, and previous MI.



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 Figure 11-12 Complications of MI. **A-C**, Cardiac rupture. **A**, Anterior myocardial rupture in an acute infarct (arrow). **B**, Complete rupture of a necrotic papillary muscle. **C**, Complete rupture of a necrotic papillary muscle. **D**, Fibrinous pericarditis, showing a dark, roughened epicardial surface. **E**, Expansion of anteroapical infarct with wall thinning (arrow) and mural thrombus. **F**, Large apical left ventricular aneurysm. *Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles*. Philadelphia, WI

Nearly three-fourths of patients have one or more complications after acute MI (some are illustrated in Figure 11-12A).

**Contractile dysfunction.** An MI affects left ventricular pump function approximately proportionally to the degree of left ventricular failure, with hypotension, pulmonary vascular congestion, and fluid in the interstitial and alveolar spaces. Severe "pump failure" (*cardiogenic shock*) occurs in 10% to 20% of patients with a large infarct (often >40% of the left ventricle). Cardiogenic shock has a nearly 70% rate of in-hospital deaths. **Arrhythmias.** Following an MI, many patients develop arrhythmias, which are a major cause of the sudden deaths. MI-associated arrhythmias include sinus bradycardia, heart block, premature ventricular contractions or ventricular tachycardia, and ventricular fibrillation. **Myocardial rupture.** Rupture occurs in 1% and 5% of MIs but is a frequent cause (7% to 25%) of MI-associated demise. Complications include (1) free wall, with hemopericardium and cardiac tamponade, usually fatal (Fig. 11-12A); (2) rupture of the septum, forming a new VSD and left-to-right shunt (Fig. 11-12B); and (3) papillary muscle rupture, resulting in acute mitral regurgitation (Fig. 11-12C). Rupture can occur at almost any time after MI but is most common 3 to 7 days after MI, during the process that lysis of the myocardial connective tissue is maximal and the granulation tissue is forming a matrix to buttress the wall. Risk factors for free-wall rupture include age older than 60 years, hypertension, lack of left ventricular hypertrophy, and no previous MI (pre-existing scarring and tearing). **Pericarditis.** A fibrinous or hemorrhagic pericarditis usually develops within 2 to 3 days after MI and spontaneously resolves with time (Fig. 11-12D); it is the epicardial manifestation of the underlying myocardial necrosis and expansion. Because of the weakening of necrotic muscle, there may be disproportionate size of the infarct region (especially with anteroseptal infarcts); this is often associated with mural thrombus in the infarct, the combination of a local loss of contractility (causing stasis) with endocardial surface irregularities can foster *mural thrombosis* (Chapter 4) and, potentially, *thromboembolism* (Fig. 11-12E). Complications, aneurysms of the ventricular wall most commonly result from a large transmural infarct with formation of thin scar tissue (Fig. 11-12F). Complications of ventricular aneurysms include heart failure, but rupture of the fibrotic wall does not occur. **Papillary muscle dysfunction.** As mentioned, papillary muscle rupture after MI occurs rarely as a result of rupture. More frequently, postinfarct mitral regurgitation results from dysfunction of a papillary muscle and underlying myocardium, and later from papillary muscle dilation. **Progressive late heart failure** is discussed as chronic IHD below.

*The risk of developing complications and the prognosis after MI depend on infarct size, site, and whether the infarct is subendocardial or transmural.* Large transmural infarcts have a higher probability of complications, including arrhythmias, and late CHF. Patients with anterior transmural infarcts are at greatest risk for free-wall rupture, mural thrombus, and aneurysm. In contrast, posterior transmural infarcts are more likely to be complicated by serous effusion, pericarditis, or both; when acute ventricular septal defects occur in this area they are more difficult to repair. Anterior infarcts have a substantially worse clinical course than those with posterior infarcts. Anterior infarcts form on the endocardial surface, but pericarditis, rupture, and aneurysms rarely occur.

Long-term prognosis after MI depends on many variables, the most important of which are the quantity and extent of vascular obstructions in vessels that perfuse the remaining viable myocardium. The overall mortality is about 30%, including those who die before reaching the hospital. Thereafter, there is a 3% to 4% annual mortality.

### Chronic Ischemic Heart Disease

Chronic IHD, also called *ischemic cardiomyopathy*, is essentially progressive heart failure as a consequence of myocardial damage. In most instances there is a history of MI. Chronic IHD usually results from postinfarction remodeling and exhaustion of the hypertrophy of the viable myocardium. In other cases severe obstructive CAD results in chronic ischemia with diffuse myocardial dysfunction.

#### Morphology

Hearts from patients with chronic IHD are usually **enlarged** and heavy from **left ventricular hypertrophy**. Invariably there is moderate to severe atherosclerosis of the coronary arteries, with total or near-total occlusion. Discrete, gray-white scars of healed infarcts are usually present. The size of the scars is proportional to the size of the infarct. The scars are usually located in the subendocardial region, but they may be transmural. The scars are usually located in the subendocardial region, but they may be transmural.



shows patchy, fibrous thickening, and mural thrombi may be present. The major myocardial changes are myocardial hypertrophy, diffuse subendocardial myocyte vacuolization, and fibrosis.

### *Clinical Features*

Chronic IHD is characterized by the development of severe, progressive heart failure, sometimes arrhythmias are common and, along with CHF and intercurrent MI, account for many deaths.

### **Sudden Cardiac Death (SCD)**

Affecting some 300,000 to 400,000 individuals annually in the United States, SCD is most common among young adults. Cardiac causes either without symptoms or within 1 to 24 hours of symptom onset (different authors). Coronary artery disease is the most common underlying cause, and in many adults SCD is the first clinical manifestation of atherosclerosis. In young victims other nonatherosclerotic causes are more common:

Congenital coronary arterial abnormalities  
Aortic valve stenosis  
Mitral valve prolapse  
Myocarditis  
Cardiomyopathy  
Pulmonary hypertension  
Hereditary or acquired abnormalities of the cardiac conduction system  
The most important cause is the autosomal dominant long-QT syndrome, due to mutations in various genes. In some cases, SCD is caused by hypertrophy, hypertensive or of unknown cause. Increased cardiac mass is an independent risk factor. In young individuals who die suddenly (including athletes) have unsuspected hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and abnormalities of coronary arteries.

*The ultimate mechanism of SCD is most often a lethal arrhythmia, such as ventricular fibrillation. In many cases, structural heart pathologies, can directly affect the conduction system, most cases of fatal arrhythmia are triggered by structural changes distant from the conduction system. The prognosis of patients vulnerable to SCD, especially those with structural heart disease, is poor. The use of automatic cardioverter defibrillators, which sense and electrically terminate episodes of ventricular tachycardia or fibrillation, can improve survival.*

### **Morphology**

Severe coronary atherosclerosis with critical ( $\geq 75\%$ ) stenosis involving one or more vessels is present in 80% to 90% of SCD victims; acute plaque disruption is found in many of these. A healed MI is present in about 40%, but in those who were successfully resuscitated after cardiac arrest, new MI is found in only 25% or less. Subendocardial myocyte vacuolization and severe chronic ischemia is common. Only a minority (10% to 20%) of cases of SCD are of noncardiac origin.

### **SUMMARY**

#### **Ischemic Heart Disease**

The vast majority of ischemic heart disease is due to coronary artery atherosclerosis. Frequent contributions of vasospasm, vasculitis, or embolism. Cardiac ischemia results from an imbalance between coronary supply and myocardial demand, and presents as different, albeit related, clinical syndromes. *Angina pectoris* is chest pain due to inadequate perfusion and is typical of atherosclerotic disease with  $\geq 75\%$  fixed stenosis (so-called critical stenosis). *Unstable angina* is caused by a small fissure or rupture of atherosclerotic plaque triggering platelet aggregation, vasoconstriction, and formation of a mural thrombus that may not be occlusive. *Myocardial infarction* typically results from acute thromboses that follow plaque disruption. *Sudden cardiac death* results from a fatal arrhythmia, most often in the setting of severe coronary artery disease. *Chronic ischemic heart disease* is the result of myocardial damage due to ischemic injury, either from prior infarction(s) or chronic low-grade ischemia. Ischemia to myocardium rapidly (minutes) leads to loss of function and causes irreversible damage within minutes. The diagnosis of MI is based on symptoms, electrocardiographic changes, and measurement of serum CK-MB and troponins. Gross and histologic changes take hours to days to develop. Complications of infarction include rupture of ventricular wall, papillary muscle; aneurysm formation; mural thrombus; arrhythmia; pericarditis.



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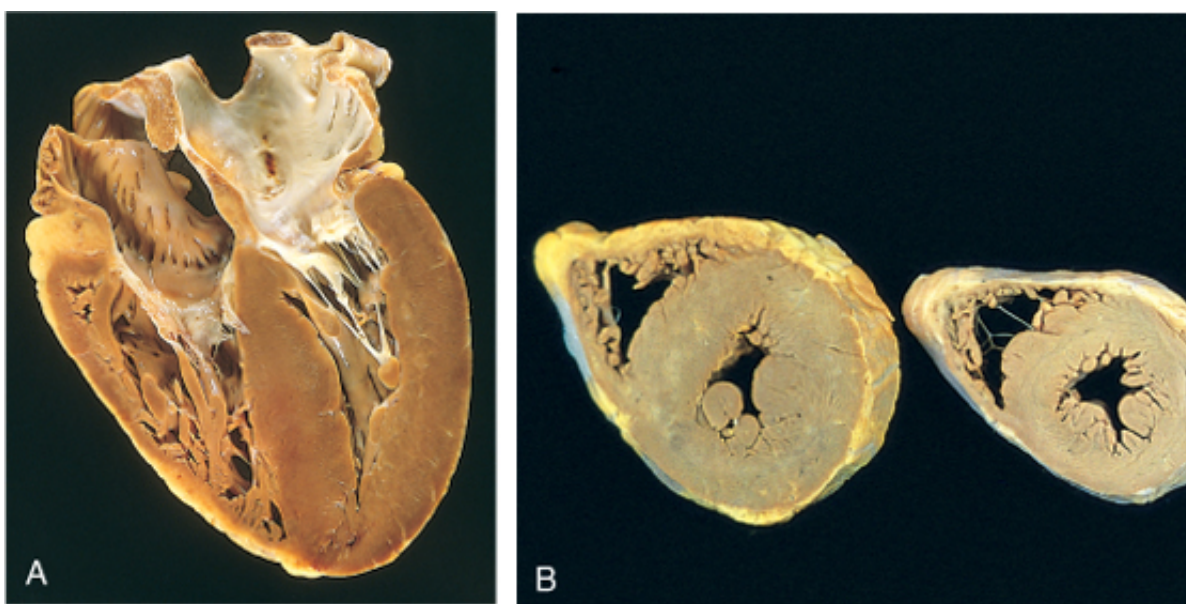
## HYPERTENSIVE HEART DISEASE

As discussed in [Chapter 10](#), chronic hypertension is a common disorder associated with considerable morbidity including heart, brain, and kidneys. We will begin this section by first discussing the pathophysiology of cardiac hypertrophy, though such hypertrophy can be caused by many stressors in addition to hypertension. The common cardiac complications of hypertension and will consider the effects of high blood pressure systemically (hypertension) and pulmonary hypertension (*cor pulmonale*).

### The Pathophysiology of Cardiac Hypertrophy

Cardiac myocytes are terminally differentiated cells without the capacity to divide; consequently, they cannot occur in response to exogenous stresses. Instead, increased work—resulting from pressure signals (e.g., hyperthyroidism)—induces an increased myocyte mass and heart size (*hypertrophy*).

The extent of hypertrophy varies with the underlying cause. Thus, heart weights usually range from normal in pulmonary hypertension and IHD, from 400 to 800 gm (two to three times normal) in systemic hypertension, mitral regurgitation, or dilated cardiomyopathy, and from 600 to 1000 gm (three to four times normal) in aortic stenosis.



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Figure 11-13 Left ventricular hypertrophy (LVH). **A**, Pressure hypertrophy due to left ventricular outflow obstruction, apical four-chamber view of the heart. **B**, Altered cardiac configuration in LVH without and with dilation, viewed in cross-section. **Center**, normal heart; **left**, the pressure-hypertrophied heart has increased mass and a thick left ventricular wall; **right**, the volume-overloaded heart has increased mass but a normal wall thickness. (From Edwards WD: Cardiac anatomy and examination, 5th ed. Philadelphia, Williams & Wilkins, 1995, p 86.)

The pattern of hypertrophy reflects the nature of the initiating stimulus ([Fig. 11-13](#)). *Pressure-overload* (e.g., aortic valve stenosis) develops *concentric hypertrophy*, with an increased wall thickness; in the left ventricle, this can even reduce the cavity diameter. In contrast, *volume overload* (e.g., aortic valve insufficiency) is characterized by ventricular dilation. In volume overload, muscle mass increases roughly in proportion to chamber size. In dilated hearts there can actually be a substantial hypertrophy without increased wall thickness. This is an inadequate measure of hypertrophy due to volume overload.

*While initially compensatory, prolonged or excessive hypertrophy can eventually result in myocyte structural, biochemical, and molecular bases for this failure remain obscure. What is known is that numerous changes in gene expression, typically with patterns of protein synthesis recapitulating fetal isoforms of proteins may either be less functional than the adult isoforms, or may be expressed in intracellular handling of calcium ions could conceivably contribute to impaired contraction and relaxation not accompanied by a commensurate increase in the vascular supply. Thus, there is a relative decrease in coronary blood flow. Chronic ischemia causes deposition of fibrous tissue, which limits diastolic relaxation. At the same time, there are increased metabolic requirements that increase oxygen consumption. This sequence of events leads to decompensation.*

### **Systemic Hypertensive Heart Disease**

Systemic hypertensive heart disease is diagnosed when there is (1) left ventricular hypertrophy (without a causal cardiovascular pathology (e.g., valvular stenosis), and (2) a history or pathologic evidence of left ventricular hypertrophy. Study established unequivocally that even mild hypertension (levels only slightly above 140/90 mmHg) is associated with left ventricular hypertrophy. Roughly 25% of the US population suffers from at least this degree of

#### **Morphology**

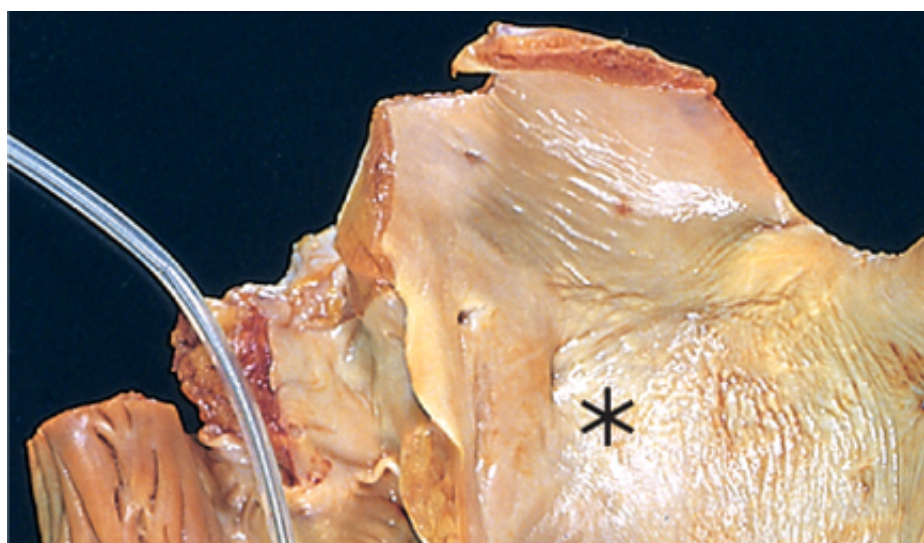
The essential feature of hypertensive heart disease is left ventricular hypertrophy, with or without dilation (Fig. 11-14). The left ventricular wall thickness may exceed 2.0 cm and the weight may exceed 500 gm. In time, the increased thickness of the left ventricular wall imparts a stiffening of the ventricle, which often induces left atrial enlargement.

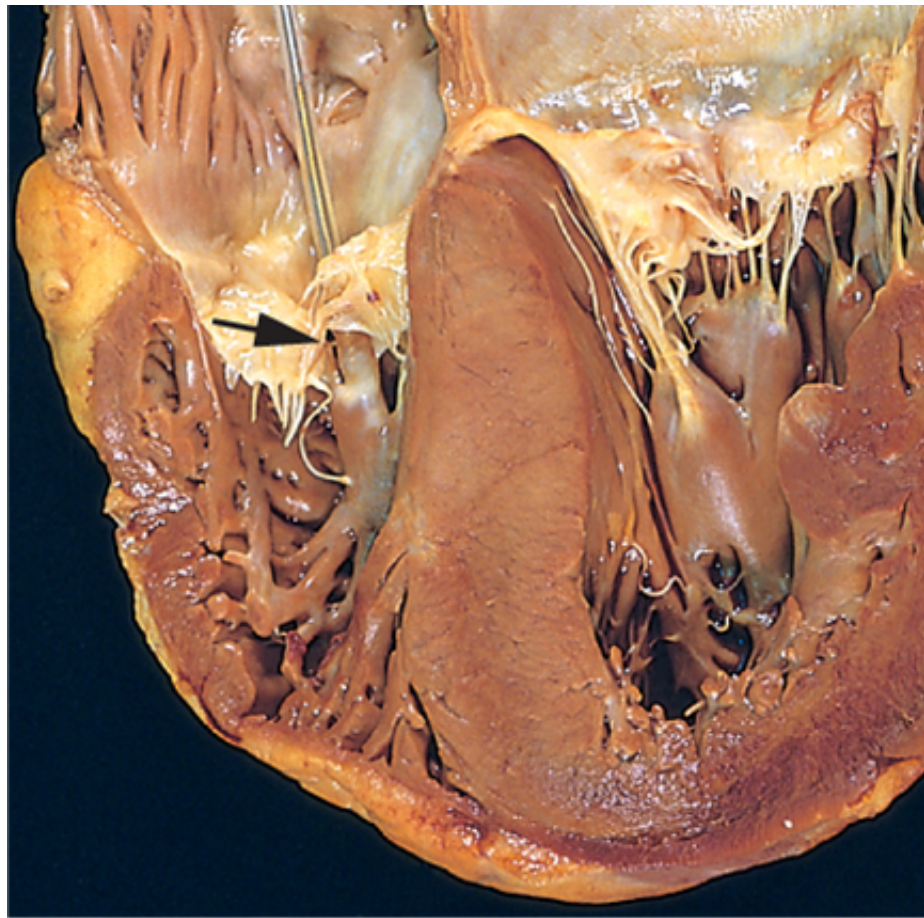
Microscopically, myocyte diameter increases, typically associated with prominent, eosinophilic nuclei, nuclear enlargement and hyperchromasia ("box-car nuclei"); there is also increase in interstitial fibrosis.

#### **Clinical Features**

Compensated hypertensive heart disease may be asymptomatic and suspected only by electrocardiographic indications of left ventricular hypertrophy. In a subset of patients, the disease comes to attention clinically as a result of left atrial enlargement (resulting from left atrial enlargement) and/or CHF. Depending on the severity, duration, and under adequacy of therapeutic control, the patient may (1) enjoy normal longevity and die of unrelated causes, (2) develop atherosclerotic disease potentiating coronary atherosclerosis, (3) suffer progressive renal damage or cerebrovascular stroke, or (4) die of heart failure. As mentioned earlier, increased cardiac mass is an independent risk factor for sudden cardiac death. Treatment of hypertension can prevent or lead to regression of cardiac hypertrophy and its associated risks.

### **Pulmonary Hypertensive Heart Disease (Cor Pulmonale)**





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Figure 11-14 Hypertensive heart disease with marked concentric thickening of the left ventricular wall causing right in this apical four-chamber view of the heart. A pacemaker is incidentally present in the right ventricle (arrow) relative stiffening of the left ventricle causing impaired diastolic relaxation and subsequent

*Cor pulmonale* consists of right ventricular hypertrophy and dilation due to *pulmonary hypertension* *parenchyma* or *pulmonary vasculature* (Table 11-3). Generally, right ventricular dilation and hypertrophy due to left ventricular failure are excluded by this definition.

*Cor pulmonale* may be acute or chronic, depending on the tempo by which the pulmonary hypertension occurs. It most commonly follows massive pulmonary embolism with obstruction of >50% of the pulmonary vasculature. It can also occur secondary to prolonged pressure overload caused by obstruction of the pulmonary vasculature or septal capillaries (resulting from emphysema, interstitial pulmonary fibrosis, or primary pulmonary hypertension).

Table 11-3. Disorders Predisposing to Cor Pulmonale

Diseases of the Pulmonary Parenchyma
Chronic obstructive pulmonary disease
Diffuse pulmonary interstitial fibrosis
Pneumoconioses
Cystic fibrosis
Bronchiectasis
Diseases of the Pulmonary Vessels
Recurrent pulmonary thromboembolism
Primary pulmonary hypertension
Extensive pulmonary arteritis (e.g., Wegener's granulomatosis)



Extensive pulmonary arteritis (e.g., Wegener granulomatosis)

Drug-, toxin-, or radiation-induced vascular obstruction

Extensive pulmonary tumor microembolism

#### **Disorders Affecting Chest Movement**

Kyphoscoliosis

Marked obesity (pickwickian syndrome)

Neuromuscular diseases

#### **Disorders Inducing Pulmonary Arterial Constriction**

Metabolic acidosis

Hypoxemia

Chronic altitude sickness

Obstruction to major airways

Idiopathic alveolar hypoventilation

#### **Morphology**

In acute cor pulmonale the right ventricle is usually dilated but does not show hypertrophy. In chronic cor pulmonale the right ventricle is dilated and hypertrophied. In acute cor pulmonale the heart may even be of normal size. Chronic cor pulmonale is characterized by right ventricular (and often right atrial) hypertrophy. In extreme cases the thickness of the right ventricular wall may be comparable to or even exceed that of the left ventricle (Fig. 11-15). When ventricular dilation is severe, the right ventricle and atrium may also be dilated. Such dilation may mask right ventricular hypertrophy. Chronic cor pulmonale occurs in the setting of chronically elevated pulmonary artery pressure. Pulmonary arteries often contain atheromatous plaques and other lesions reflecting systemic hypertension (Chapter 13).

#### **SUMMARY**

##### **Hypertensive Heart Disease**

Hypertensive heart disease can affect either the left or the right ventricle; the left ventricle is more commonly affected. The response of the heart to increased pressures is myocyte hypertrophy and hyperplasia. In the left ventricle, pressure overload, as with hypertension or aortic stenosis, results in concentric hypertrophy. In the right ventricle, volume overload (e.g., valvular incompetence), results in eccentric hypertrophy. The mechanisms that result in heart failure due to hypertension are not fully understood; they probably involve the synthesis of relatively less efficient myofibrils and a diminished vascular supply relative to the increased myocyte mass. Cor pulmonale is a form of right ventricular hypertensive heart disease caused by primary disorders of lung parenchyma (e.g., chronic obstructive pulmonary disease) and pulmonary vasculature.





## VALVULAR HEART DISEASE



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Figure 11-15 Chronic cor pulmonale, characterized by a markedly dilated and hypertrophied right ventricle, with the

(apical four-chamber view of heart, right ventricle on *left*). The shape of the left ventricle (to the *right*) has been compared with Figure 11-16.

Valvular disease results in stenosis or insufficiency (regurgitation or incompetence), or both.

*Stenosis is the failure of a valve to open completely, obstructing forward flow.* Valvular stenosis is caused by a primary cuspal abnormality (e.g., calcification or valve scarring). *Insufficiency results from either int* valve destruction) or distortion of the supporting structures (e.g., the aorta, mitral annulus, or ventricular free wall) without primary changes in the cusps. It can appear acutely, as with c leaflet scarring and retraction.

Stenosis or regurgitation can occur in pure forms, or may coexist in the same valve. Valvular disease of the mitral valve is most commonly affected), or more than one valve. The outcome of valvular disease depends on the degree of impairment, the tempo of its development, and the rate and quality of compensatory mechanisms. Destruction of an aortic valve cusp by infection may cause massive regurgitation and rapid cardiac failure. Aortic stenosis usually develops over years, and its clinical effects are remarkably well tolerated. Abnormal heart sounds called *murmurs*.

Valve abnormalities can be caused by congenital disorders or by a variety of acquired diseases. The major valve diseases are summarized in Table 11-4; *acquired stenoses of the aortic and mitral valves are the most common valve disease*.

### Calcific Aortic Stenosis

Degenerative changes in the cardiac valves are an almost inevitable part of the aging process, given which they are subjected during life (>40 million cardiac cycles per year with substantial deformation). Calcification and calcification can be thought of as valvular counterparts of age-related arteriosclerosis.

The most common degenerative valvular disease is calcific aortic stenosis. *It is the most common valvular disease* and is usually the consequence of calcification from progressive age-associated "wear and tear" on the valves or congenitally bicuspid valves (Fig. 11-16). *Congenitally bicuspid valves* (i.e., valves with two cusps) have an estimated frequency of approximately 1.4% of live births. The two cusps are usually of unequal size, the smaller one being the *raphe*, resulting from incomplete cuspal separation during development. Bicuspid aortic valves are usually symptomatic throughout early life. However, they are more prone to progressive degenerative calcification. *Calcification* primarily involves the valve annulus and is usually asymptomatic unless the calcification is severe (Fig. 11-6C, D).

**Table 11-4. Major Etiologies of Acquired Heart Valve Disease**

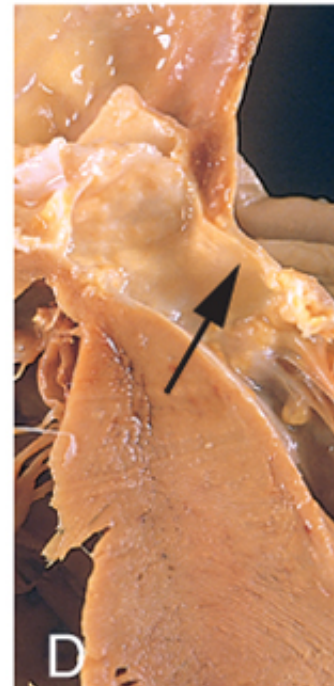
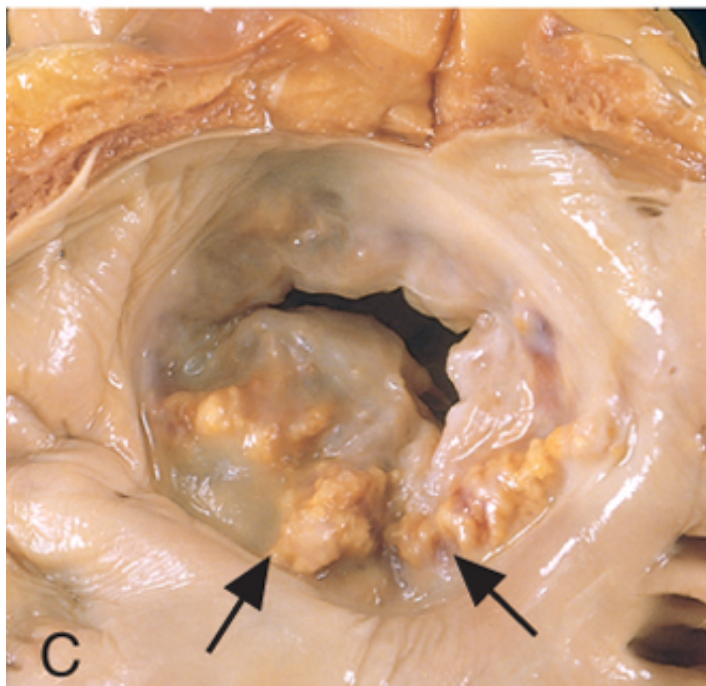
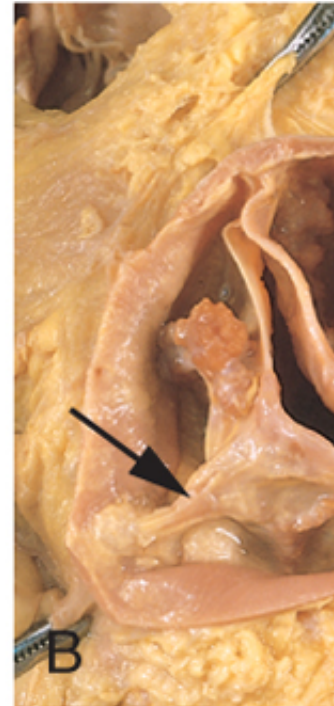
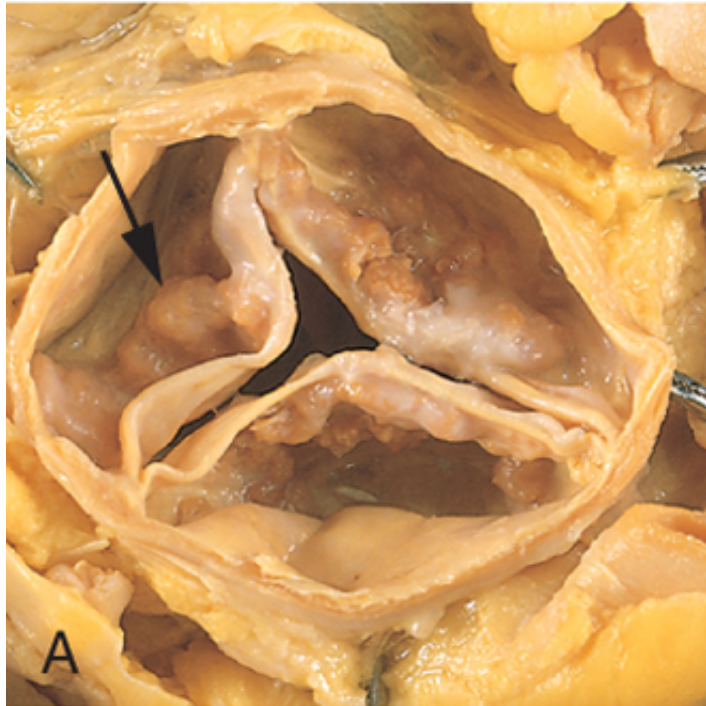
<b>Mitral Valve Disease</b>	<b>Aortic Valve Disease</b>
<b>Mitral Stenosis</b>	<b>Aortic Stenosis</b>
Postinflammatory scarring (rheumatic heart disease)	Postinflammatory scarring Senile calcific aortic stenosis Calcification of congenitally bicuspid aortic valve
<b>Mitral Regurgitation</b>	<b>Aortic Regurgitation</b>
<b>ABNORMALITIES OF LEAFLETS AND COMMISSURES</b>	<b>INTRINSIC VALVULAR DISEASE</b>
Postinflammatory scarring	Postinflammatory scarring (rheumatic heart disease)
Infective endocarditis	Infective endocarditis
Mitral valve prolapse	
Fen-phen-induced valvular fibrosis	
<b>ABNORMALITIES OF TENSOR APPARATUS</b>	<b>AORTIC DISEASE</b>
Rupture of papillary muscle	Degenerative aortic regurgitation
Papillary muscle dysfunction (fibrosis)	Syphilitic aortitis Ankylosing spondylitis



Rupture of chordae tendineae	Rheumatoid arthritis
	Marfan syndrome
<b>ABNORMALITIES OF LEFT VENTRICULAR CAVITY AND/OR ANNULUS</b>	
LV enlargement (myocarditis, dilated cardiomyopathy)	
Calcification of mitral ring	

LV, left ventricular.

Modified from Schoen FJ: Surgical pathology of removed natural and prosthetic valves. Hum Pathol 18:558, 1987.







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Figure 11-16 Calcific valvular degeneration. **A**, Calcific aortic stenosis of a previously normal valve having three cusps. The cusps are heaped up within the sinuses of Valsalva (*arrow*). Note that the commissures are not fused, as in mitral stenosis. **B**, Calcific aortic stenosis occurring on a congenitally bicuspid valve. One cusp has a partial fusion at its center, with calcific nodules at the base (attachment margin) of the anterior mitral leaflet (*arrows*). **C**, Left atrial valve, showing leaflet and annular calcification.

The incidence of calcific aortic stenosis is increasing with the rising average age of the US population. The disease typically begins to manifest when patients reach their 70s and 80s; onset with bicuspid aortic valve is earlier.

### Morphology

The hallmark of calcific aortic stenosis (with either normal or bicuspid valves) is the presence of **calcific masses** on the outflow side of the cusps; these protrude into the sinuses of Valsalva and impede valve opening (see Fig. 11-16A); commissural fusion is not a usual feature of aortic stenosis, although the cusps may become secondarily fibrosed and thickened. An inconsequential stage of the calcification process is called aortic valve sclerosis. In severe disease, significant outflow obstruction leads to left ventricular pressure overload with consequent left ventricular hypertrophy and dilation.

### Clinical Features

In severe calcific aortic stenosis, valve orifices can be compromised by as much as 70% to 80%. The resulting obstruction leads to left ventricular pressures as high as 200 mm Hg or more; cardiac output is markedly reduced, and left ventricular hypertrophy develops. The hypertrophied myocardium tends to be relatively ischemic (see discussion of coronary artery disease), and angina can develop. Syncope may develop due to poor perfusion of the brain. Systemic hypertension may cause CHF, and cardiac decompensation eventually ensues. The onset of symptoms (angina, CHF, or syncope) marks the exhaustion of compensatory cardiac hyperfunction and carries a poor prognosis if not treated surgically (aortic valve replacement).

### Myxomatous Mitral Valve

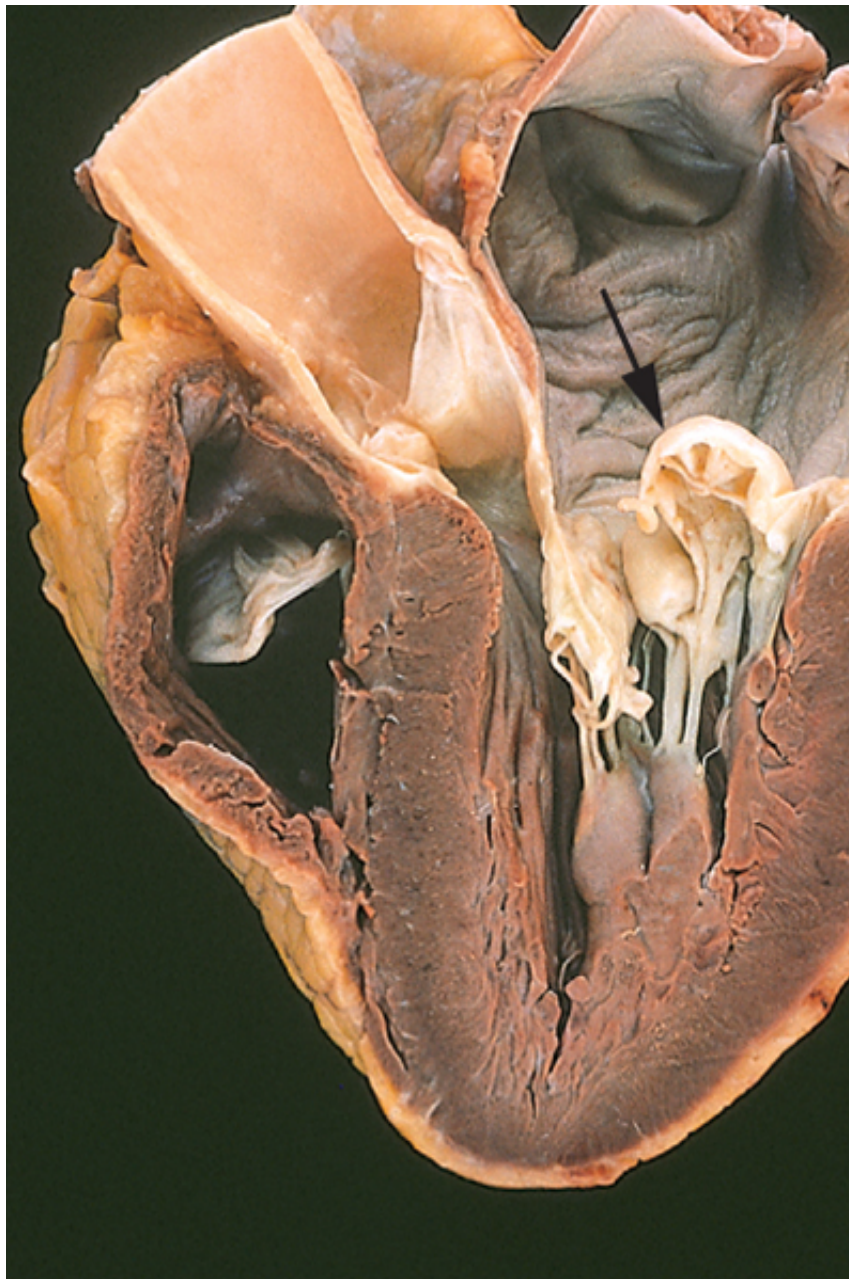
In *myxomatous degeneration of the mitral valve*, one or both mitral leaflets are "floppy" and *prolapse* (bulge) back into the left atrium during systole. *Mitral valve prolapse* is a primary form of myxomatous mitral degeneration. It is the most common valvular disease in the United States, women seven times more frequently than men; as such, it is one of the most common cardiovascular diseases in the industrialized world. Secondary myxomatous mitral degeneration can occur in any of a number of systemic diseases caused by some other entity (e.g., IHD).

### Morphology

Myxomatous degeneration of the mitral valve is characterized by ballooning (hooding) of the leaflets (Fig. 11-17). The affected leaflets are enlarged, redundant, thick, and rubbery; they may also be elongated, thinned, and occasionally ruptured. In mitral valve prolapse, concentric left ventricular hypertrophy and dilation are common (20% to 40% of cases), and aortic and pulmonic valves can be affected. Histologically, the essential change is thinning of the fibrosa layer of the valve, on which the integrity of the leaflet depends, accompanied by expansion of the middle spongiosa by deposition of myxomatous (mucoid) material. The same changes occur whether the degeneration is due to an intrinsic defect (primary) or is caused by regurgitation due to aortic stenosis or ischemic dysfunction).

### Pathogenesis





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 Figure 11-17 Myxomatous degeneration of the mitral valve. Long axis of left ventricle demonstrating hooding with prolapse into left atrium (arrow). The left ventricle is on the right in this apical four-chamber view. (Courtesy of Dr. William D. English)

The basis for primary myxomatous degeneration of the mitral valve is unknown. Nevertheless, the (possibly systemic) intrinsic defect of connective tissue—either in its synthesis or remodeling. Thus mitral valve prolapse is a common feature of Marfan syndrome (due to fibrillin-1 mutations; [Chapter 7](#)) and occurs in other connective tissue disorders. In some patients, there are additional hints of systemic connective tissue structural abnormalities, such as arched palates. Subtle defects in structural proteins or the cells that make them may predispose for certain tissues (e.g., cardiac valves) to defective synthesis or catabolism of extracellular matrix. Secondary mitral valve prolapse results from "degenerative" changes in the valve myofibroblasts, responding to chronically aberrant hemodynamic forces.

#### *Clinical Features*

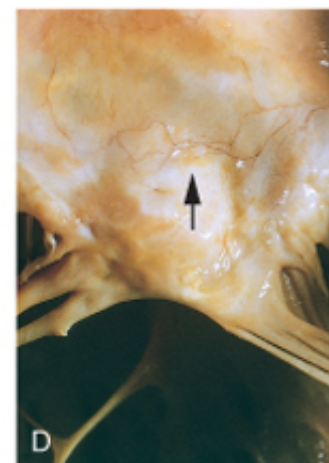
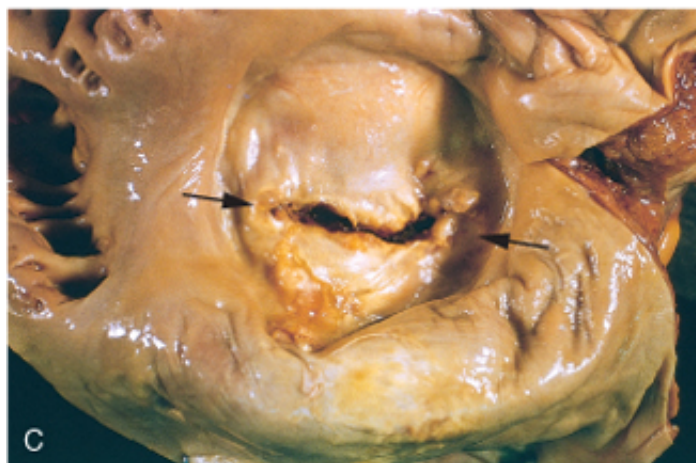
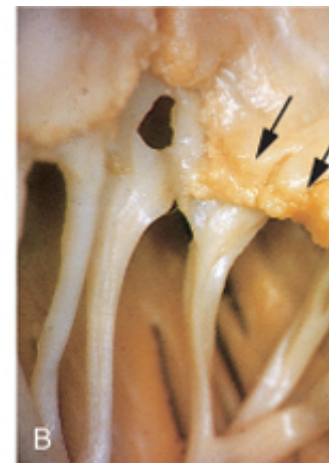
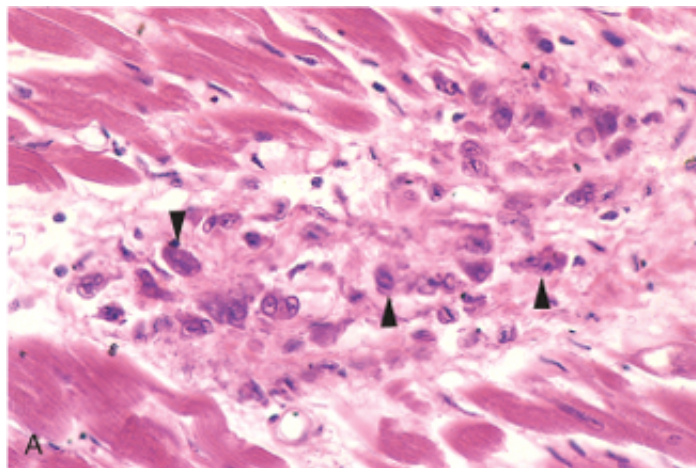
Most patients with mitral valve prolapse are asymptomatic, and the valvular abnormality is usually detected on echocardiographic examination. A minority of patients may complain of palpitations, dyspnea, or atypical chest pain.

caused by abrupt tension on the redundant valve leaflets and chordae tendineae as the valve attains an associated regurgitant murmur. Although the majority of patients with mitral valve prolapse have approximately 3% experience one of several complications. These include hemodynamically significant mitral regurgitation, particularly if the chordae or valve leaflets rupture. Patients with mitral valve prolapse and valvular disease are at risk for the development of infective endocarditis (see below) and sudden death caused by ventricular infarction may occur from embolism of thrombi formed in the left atrium.

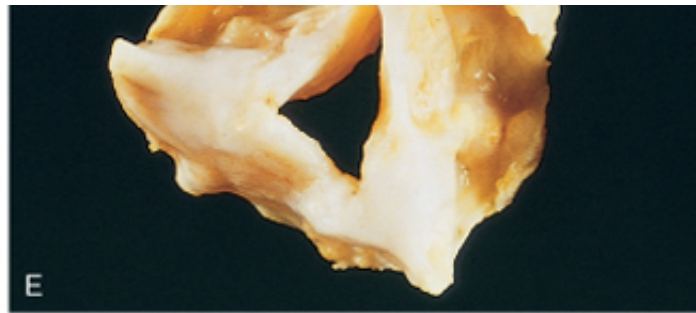
### Rheumatic Valvular Disease

Rheumatic fever (RF) is an acute, immunologically mediated, multisystem inflammatory disease that follows group A  $\beta$ -hemolytic streptococcal pharyngitis; it can also rarely occur with streptococcal infection of the skin. Rheumatic heart disease (RHD) is the cardiac manifestation of RF and is associated with inflammation of the heart muscle and pericardium.

Chronic valvular deformities are the most important consequences of RHD; these are characterized by thickening and fusion of the valve leaflets, resulting in permanent dysfunction (mitral stenosis being most common). The incidence of RF, and hence RHD, has declined in the industrialized world over the past 30 years; this is due to a combination of improved socioeconomic conditions, widespread treatment of streptococcal pharyngitis, and a fortuitous (and unexplained) decline in the virulence of the organism. In economically depressed urban areas or developing countries, RF and RHD remain important public health problems.







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Figure 11-18 Acute and chronic rheumatic heart disease. **A**, Microscopic appearance of an Aschoff body in a patient with acute rheumatic fever, showing fibrinoid necrosis with a circumscribed collection of mononuclear inflammatory cells, with some activated macrophages (arrowheads). **B**, Acute rheumatic mitral valvulitis superimposed on chronic rheumatic heart disease. Small vegetations (arrows) are seen on the mitral valve leaflet. Previous episodes of rheumatic valvulitis have caused fibrous thickening and stenosis with diffuse fibrous thickening and distortion of the valve leaflets, commissural fusion (arrows), and thickening of the chordae tendineae. **C**, Closed mitral valve. Note the thickened leaflets and the small vegetations (arrows). **D**, Opened valve. Note neovascularization of anterior mitral leaflet (arrow). **E**, Surgically removed specimen of rheumatic heart disease showing distortion of the cusps with commissural fusion (**E**, From Schoen FJ, St. John-Sutton M: Contemporary issues in rheumatic heart disease. *N Engl J Med* 356:1049-1056, 2007.)

### Morphology

The cardiac manifestations of acute RF and chronic RHD are shown in Fig. 11-18. In acute RF, inflammatory lesions are found in various tissues throughout the body. Within the heart, the lesions are called **Aschoff bodies** and are pathognomonic for RF (Fig. 11-18A). Aschoff bodies consist of a central area of fibrinoid necrosis surrounded by a ring of inflammatory cells, including lymphocytes, plasma cells, and plump activated macrophages called **Anitschkow cells**. The Anitschkow cells have an abundant cytoplasm and central nuclei with chromatin arrayed in a slender, wavy pattern (Fig. 11-18A); these activated macrophages can also fuse to form giant cells. Aschoff bodies are found in all three layers of the heart—pericardium, myocardium, or endocardium (including valvular involvement)—a condition called **pancarditis**. The pericardium shows a fibrinous or serofibrinous exudate, which gives rise to the characteristic "fish mouth" appearance of the heart in acute RF. The myocardial involvement (myocarditis) takes the form of scattered Aschoff bodies in the interstitial connective tissue. Valve involvement results in fibrinoid necrosis along the leaflets (Fig. 11-18B) forming 1- to 2-mm vegetations (verrucae) that have little effect on cardiac function. Warty projections probably arise from the precipitation of fibrin at sites of erosion caused by inflammation and collagen degeneration.

**Chronic RHD** is characterized by organization of the acute inflammation and subsequent fibrosis. The cardinal anatomic changes of the mitral (or tricuspid) valve include leaflet thickening, shortening, and thickening and fusion of the chordae tendineae (Fig. 11-18C-D). Fibrous bands between the valvular commissures and calcification create "fish mouth" or "buttonhole" stenosis. Microscopically there is neovascularization (grossly evident in Fig. 11-18D), with destruction of the normal leaflet architecture. Aschoff bodies are replaced by fibrous scar tissue. These lesions are rarely seen in chronic RHD.

The functional consequence of RHD is **valvular stenosis and regurgitation** (stenosis predominates); indeed, RHD is overwhelmingly the most frequent cause of mitral stenosis. The **mitral valve alone is involved in 70% of cases** of RHD, with combined mitral and aortic disease in another 25%; the tricuspid valve is usually less frequently and less severely involved, and the pulmonic valve almost always escapes injury. With tight mitral stenosis, the left atrium may harbor **mural thrombi**. Long-standing congestive changes in the lungs may lead to right ventricular hypertrophy and pulmonary hypertension. With mitral stenosis, the left ventricle is generally normal.

### Pathogenesis



Acute RF is a hypersensitivity reaction induced by host antibodies elicited by group A streptococci. The pathogenesis remains uncertain despite years of investigation. It appears that the M proteins of certain antibodies that cross-react with glycoprotein antigens in the heart, joints, and other tissues. This occurs some time after the original infection, and the absence of streptococci in the lesions. Since only a small percentage of people ever experience RF (estimated at 3%), a genetic susceptibility is likely to influence the development of the disease. The proposed sequence of events in acute RHD is summarized in Fig. 11-19. The chronic sequelae result from the healing of the acute inflammatory lesions.

### Clinical Features

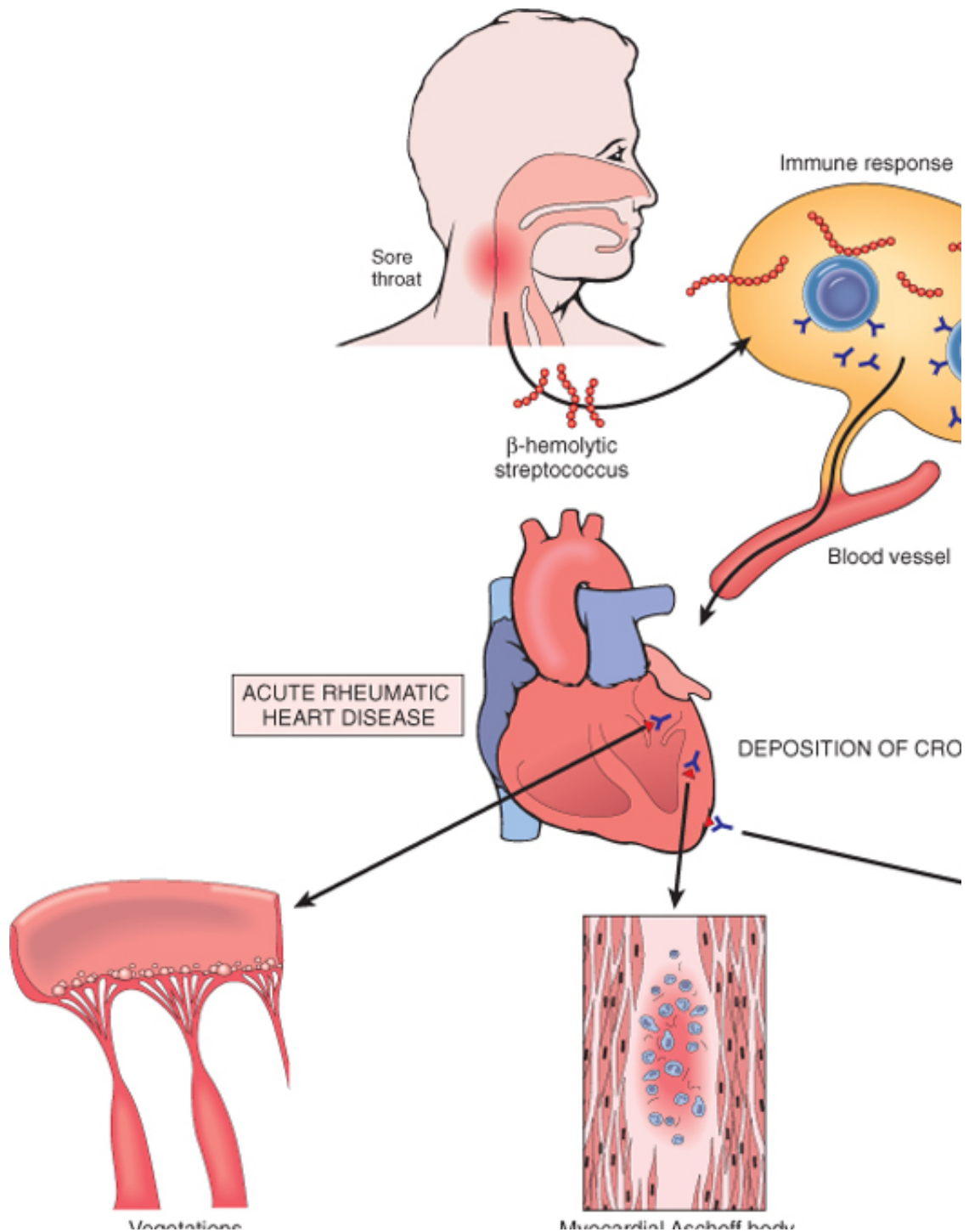


Figure 11-19 Pathogenesis and key morphologic changes of acute rheumatic heart disease. Acute rheumatic myocardium, and epicardium. Chronic rheumatic heart disease is almost always caused by deformity of the heart

Acute RF appears most often in children aged 5 to 15 years, but about 20% of first attacks occur in two to three weeks after an episode of streptococcal pharyngitis. Although cultures for streptococci begins, antibodies to one or more streptococcal antigens (streptolysin O or DNAase) can be detected. Clinical manifestations are arthritis and carditis; arthritis is far more common in adults. It typically begins accompanied by fever in which one large joint after another becomes painful and swollen for a period of time, spontaneously, leaving no residual disability. Clinical features of the carditis include pericardial friction rub can be so severe that resulting cardiac dilation causes functional mitral insufficiency and even CHF. Patients die of acute RF.

*After an initial attack there is increased vulnerability to disease reactivation with subsequent pharyngitis worsen with each recurrence, and damage is cumulative. Other hazards include embolization from vegetations on their appendages, and infective endocarditis superimposed on deformed valves. Chronic rheumatic heart disease (RHD) clinical manifestations for years or even decades after the initial episode of RF. The signs and symptoms of RHD which valve(s) are involved. As mentioned earlier, the mitral valve is the one most commonly involved in RHD. In addition to various cardiac murmurs, cardiac hypertrophy and dilation, and CHF, arrhythmias (particularly atrial fibrillation in the setting of mitral stenosis), thromboembolic complications, and subsequent infective endocarditis. The long-term prognosis is highly variable. In some cases, the deformity yielding hemodynamic abnormality, which begets further deforming fibrosis. Surgical repair has greatly improved the outlook for patients with RHD.*

Diagnosis of acute RHD is made by serologic evidence of a previous streptococcal infection, in accordance with *Jones criteria*: (1) carditis, (2) migratory polyarthritis of the large joints, (3) subcutaneous nodules, (4) erythema marginatum, and (5) Sydenham chorea, a neurologic disorder with involuntary purposeless, rapid movements. Two major manifestations and two minor manifestations (nonspecific signs and symptoms that include fever, acute-phase reactants) are also sufficient to make the diagnosis.

### Infective Endocarditis

Infective endocarditis (IE) is a serious infection requiring prompt diagnosis and intervention. It is characterized by infection of heart valves or mural endocardium—often with destruction of the underlying cardiac tissues—and is composed of necrotic debris, thrombus, and organisms. Although fungi, rickettsiae (Q fever), and the vast majority of cases are caused by extracellular bacteria.

IE is traditionally classified into *acute and subacute forms*, mostly on the basis of clinical tempo and duration, attributable to the intrinsic microbial virulence and whether underlying cardiac disease is present.

*Acute endocarditis* usually suggests a tumultuous, destructive infection, frequently involving a previously normal valve, and causing death within days to weeks in more than 50% of patients requiring surgery. *Subacute endocarditis* refers to infections by organisms of low virulence colonizing pre-existing valvular disease when there are deformed valves. The disease typically appears insidiously and follows a protracted course; most patients recovering after appropriate antibiotic therapy.

Both the clinical and morphologic patterns, however, are points along a spectrum, and a clear delineation of acute and subacute endocarditis is not always possible.

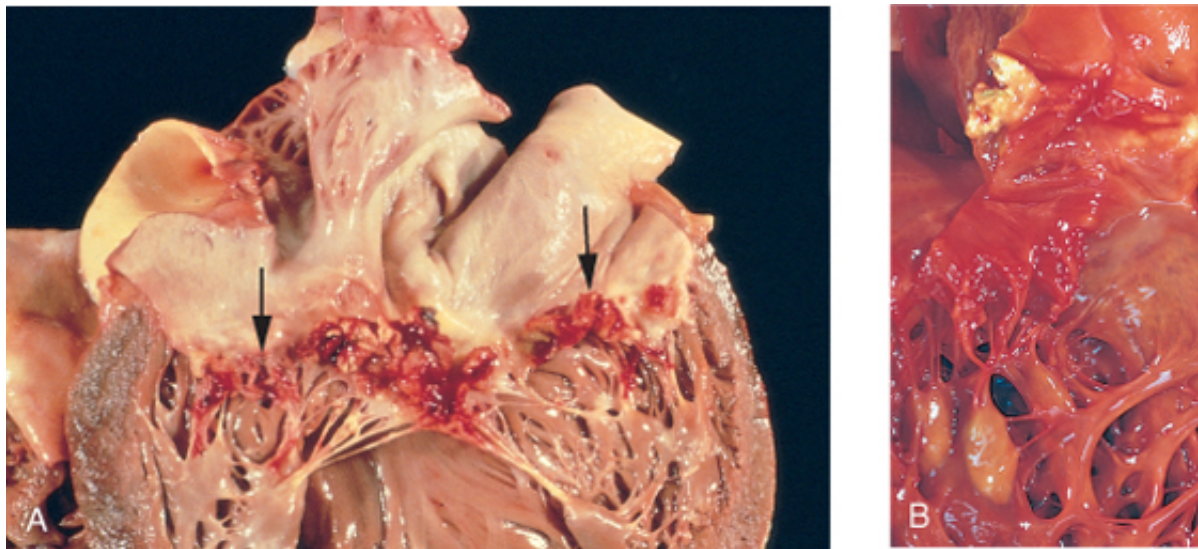
### Morphology

In both acute and subacute forms of the disease, **friable, bulky**, and potentially **debris** containing fibrin, inflammatory cells, and microorganisms are present on the heart valves. The aortic and mitral valves are the most common sites of infection, although the tricuspid valve is the most common target in the setting of intravenous drug abuse. Vegetations may be single or multiple.

than one valve; they can erode into the underlying myocardium to produce an abscess (Fig. 11-20B). The appearance of vegetations is influenced by the infecting organism's response, and antibiotic therapy. Fungal endocarditis, for example, tends to cause more extensive damage than does bacterial infection. **Systemic emboli** may occur at any time because of the friable nature of the vegetations. Because the embolic fragments contain large numbers of virulent organisms, they can develop at the sites of such infarcts (**septic infarcts**).

Subacute endocarditis is typically associated with less valvular destruction than is acute endocarditis. Microscopically, in subacute IE vegetations often have granulation tissue at their base. The degree of chronicity. As time passes, fibrosis, calcification, and a chronic inflammatory infiltrate develop.

### Pathogenesis



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Figure 11-20 Infective (bacterial) endocarditis. **A**, Endocarditis of mitral valve (subacute, caused by *Streptococcus viridans*) denoted by arrows. **B**, Acute endocarditis of congenitally bicuspid aortic valve (caused by *Staphylococcus aureus*) abscess (arrow).

IE can develop on previously normal valves, but the presence of cardiac abnormalities predispose to it. A major antecedent disorder, but it has been displaced by mitral valve prolapse, bicuspid aortic valve, and platelet-fibrin deposits at sites of jet streams caused by pre-existing cardiac disease or indwelling catheters. These sites are favorable for seeding of bacteria and development of endocarditis. With increasing use of prosthetic heart valves, they account for 10% to 20% of all cases of IE. Host factors such as neutropenia, immunodeficiency, neutrophil dysfunction, immunosuppression, diabetes mellitus, and alcohol or intravenous drug abuse also increase the risk.

The causative organisms differ depending on the underlying risk factors. Thus, endocarditis of previously normal valves is caused most commonly (50% to 60% of cases) by *viridans Streptococci*, a relatively benign organism. The more virulent *S. aureus* (common to skin) can attack *deformed and healthy* valves and is responsible for 20% to 30% of cases. It is also the major offender in intravenous drug abusers. Additional bacterial agents include enteric gram-negative bacilli (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*), all commensals in the oral flora. Fungi and bacilli and fungi are involved. In about 10% of cases, no organism can be isolated from the blood. This is attributed to previous antibiotic therapy or difficulties in isolating the offending agent, or because enlarging vegetation are not released into the blood.

Foremost among the conditions predisposing to endocarditis is seeding of the blood with microbes. The source of the bloodstream may be an obvious infection elsewhere, a dental or surgical procedure that causes bacteremia, contaminated material directly into the bloodstream by intravenous drug users, or an occult source of infection. Recognition of predisposing cardiac abnormalities and clinical conditions causing bacteria

injuries. Recognition of predisposing cardiac abnormalities and clinical conditions causing bacteria prophylaxis.

### *Clinical Features*

Fever is the most consistent sign of IE. However, in subacute disease (particularly in the elderly) manifestations may be nonspecific fatigue, weight loss, and a flulike syndrome. Splenomegaly is common. Acute endocarditis has a stormy onset with rapidly developing fever, chills, weakness, and lassitude. Multiple left-sided lesions, but these may merely relate to the pre-existing cardiac abnormality predisposing to infection. The basis of positive blood cultures, echocardiographic findings, and other clinical and laboratory findings.

Complications generally begin within the first weeks of the onset of IE. These include glomerulonephritis, antigen-antibody complexes, thus giving rise to hematuria, albuminuria, or renal failure (*glomerulonephritis*), arrhythmias (suggesting invasion into underlying myocardium), and systemic embolization all body parts. Previously common clinical findings due to microemboli are no longer seen frequently. These include nail bed, and subcutaneous nodules in the pulp of digits.

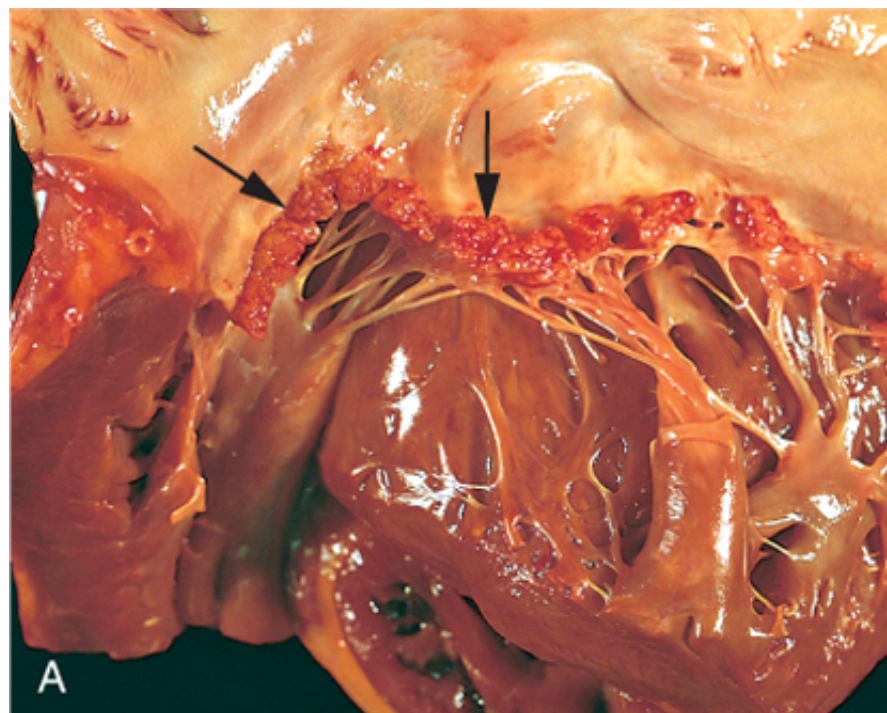
### **Noninfected Vegetations**

#### ***Nonbacterial Thrombotic Endocarditis***

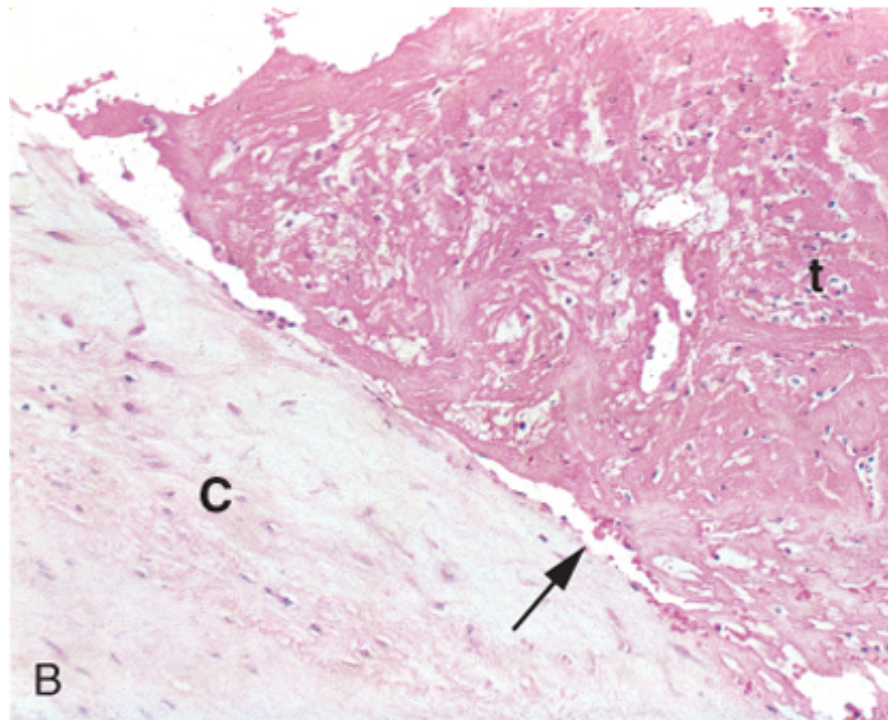
Nonbacterial thrombotic endocarditis (NBTE) is characterized by the deposition of variably sized red components on cardiac valves. In contrast to IE, the valvular lesions of NBTE are sterile and do not cause damage. Damage is not a prerequisite for NBTE; indeed, the condition is usually found on previously normal valves. In otherwise healthy individuals, a wide variety of diseases associated with general debility or wasting can be associated with NBTE, hence the alternative term *marantic endocarditis*.

#### **Morphology**

NBTE vegetations are **sterile, nondestructive, and small** (1mm); they occur singly or in small groups on the free margins of closure of the leaflets or cusps (Fig. 11-21). Histologically they are composed of fibrin and platelets, with accompanying inflammation or valve damage. With time, they can organize into dense fibrous tissue (so-called Lambl excrescences).







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Figure 11-21 Nonbacterial thrombotic endocarditis. **A**, Nearly complete row of thrombotic vegetations along the line of valve closure. **B**, Photomicrograph of nonbacterial thrombotic endocarditis, showing bland thrombus, with virtually no inflammation in the thrombus. The thrombus is only loosely attached to the cusp (arrow).

### *Pathogenesis*

NBTE typically occurs in the setting of hypercoagulable states, for example, sepsis with disseminated intravascular coagulation (DIC) (Chapter 4), hyperestrogenic states, or underlying malignancy, particularly mucinous adenocarcinomas. The procoagulant effect of circulating mucin and/or tissue factor elaborated by these tumors; indeed, NBTE is a well-recognized complication of mucinous adenocarcinoma (Chapter 6). Endocardial trauma (e.g., from an indwelling catheter) is also a well-recognized predisposing factor.

### *Clinical Features*

Although the local effect on the valve is usually trivial, NBTE lesions can become clinically significant if they obstruct the valve or embolize to other organs. NBTE can also serve as a potential nidus for bacterial colonization and thus the development of infective endocarditis.

### **Libman-Sacks Endocarditis**

Libman-Sacks endocarditis refers to sterile vegetations that can develop on the valves of patients with systemic lupus erythematosus (SLE). These lesions presumably occur because of immune complex deposition and thus have associated with SLE. Although the use of corticosteroids for treatment of lupus, Libman-Sacks endocarditis has become fairly uncommon.

### **Morphology**

The lesions in Libman-Sacks endocarditis are small sterile, granular pink vegetations that can develop on the valves of patients with SLE. They have no special predilection for the lines of valve closure and can be located on the atrioventricular valves, on the cords, or even on the atrial or ventricular endocardium. The lesions are finely granular, fibrinous eosinophilic vegetations containing nuclear debris. Fibrinoid necrosis of the valve substance adjacent to the vegetations is often present, and serious deformity can result that resemble chronic RHD.

Figure 11-22 compares the appearance of the various vegetations, including acute RHD, IE, NBTE, and Libman-Sacks endocarditis.

### **Carcinoid Heart Disease**

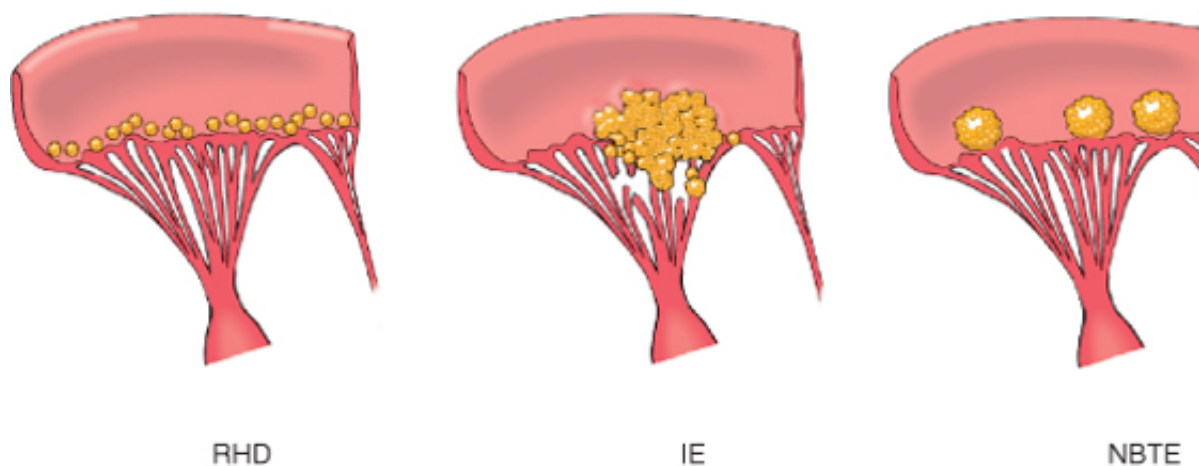
Carcinoid heart disease refers to the cardiac manifestation of a systemic syndrome that includes

Carcinoid heart disease refers to the cardiac manifestation of a systemic syndrome that includes flushing, diarrhea, and bronchoconstriction, and is caused by bioactive compounds released by *carcinoid tumors*. Cardiac involvement is a massive hepatic metastatic burden and presumably the causal mediators are no longer catabolized. The endocardium and valves of the right heart are primarily affected, because they are the first cardiac structures exposed to the substances released into the venous circulation. Carcinoid lesions on the left side of the heart can cause mitral regurgitation and right-to-left flow, or with pulmonary carcinoids.

### Morphology

The cardiovascular lesions associated with the carcinoid syndrome are distinctive, plaque-like thickenings on the endocardial surfaces of the cardiac chambers and valves. They are composed of smooth muscle cells and sparse collagen fibers embedded in an abundant extracellular matrix. Underlying structures are intact. With right-sided involvement there is tricuspid insufficiency and pulmonic stenosis.

### Pathogenesis



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Figure 11-22 Comparison of the lesions in the four major forms of vegetative endocarditis. The acute rheumatic heart disease (RHD) shows small, warty verrucae along the lines of closure of the valve leaflets. Infective endocarditis (IE) typically shows large, irregular, and friable vegetations that obscure the chordae. Nonbacterial thrombotic endocarditis (NBTE) typically shows small, bland vegetations, usually attached to the non-aortic valve surface. Libman-Sacks endocarditis (LSE) has small or medium-sized vegetations on either or both sides of the valve surface.

The mediators elaborated in carcinoid tumors include serotonin (5-hydroxytryptamine), kallikrein, histamine, and tachykinins. Although it is not clear which of these causes the lesions, plasma levels of serotonin metabolite 5-hydroxyindoleacetic acid correlate with the severity of cardiac lesions. The valvular plaques are histologically similar to the lesions that occasionally complicate the use of the appetite suppressant fenfluramine (fen-phen); interestingly, these agents affect systemic serotonin metabolism. Similar left-sided plaques have been reported in patients receiving ergotamine therapy for migraines; these drugs are metabolized to serotonin as they pass through the liver, and the damage to the valves is unknown.

### Prosthetic Cardiac Valves

Although prosthetic heart valves are less than perfect substitutes for the native tissues, their introduction has greatly benefited patients with valve disease. Two types of prosthetic valves are currently used, each with its own set of complications.

**Mechanical valves:** most commonly double tilting disk devices made of pyrolytic carbon. They require chronic anticoagulation, with the attendant risks of hemorrhage (or valve thrombosis if anticoagulation is inadequate). **Bioprosthetic valves:** made of porcine or bovine tissues, or cryopreserved human valves. These do not require anticoagulation but have a limited lifespan.

matrix deterioration. Virtually all biologic valve leaflets undergo some degree of stiffening and may be sufficient to cause significant stenosis. Calcification of bioprosthetic leaflets is also common. Bioprosthetic valves can perforate or tear, resulting in valvular insufficiency.

Prosthetic valves are also subject to infection. In mechanical valves, IE typically involves the sutures and may cause the valve to detach (*paravalvular leak*). In bioprosthetic valves, the valve leaflets can become infected.

## **SUMMARY**

### **Valvular Heart Disease**

Valve pathology can lead to occlusion (*stenosis*) and/or to regurgitation (*insufficiency*). Aortic and mitral valve stenoses account for approximately two-thirds of all valve disease. Calcification of valve substance typically results in stenosis; abnormal extracellular matrix synthesis and deposition result in myxomatous degeneration and insufficiency. Rheumatic heart disease is caused by the formation of anti-streptococcal antibodies that cross-react with cardiac tissue. Pericarditis is associated with mitral and aortic valve disease. Infective endocarditis can be aggressive and rapidly destructive (acute) or can be indolent and minimally destructive of previously abnormal valves (subacute). Systemic embolization may produce septic infarcts. Nonbacterial thrombotic endocarditis can lead to sterile vegetations on previously normal valves in states of general debility. Complications can occur.



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## CARDIOMYOPATHIES

Most cardiac disease is secondary to some other condition (e.g., coronary atherosclerosis, hypertension). However, there are some that are attributable to intrinsic myocardial dysfunction. Such myocardial diseases (literally, *heart muscle diseases*). They are a diverse group that includes inflammatory disorders (e.g., myocarditis), diseases (e.g., sarcoidosis), systemic metabolic disorders (e.g., hemochromatosis), muscular dystrophies, and degenerative diseases of muscle cells. In many cases, cardiomyopathies are of unknown etiology (termed *idiopathic*); however, some have been shown to be caused by specific genetic abnormalities in cardiac energy metabolism or contractile proteins.

Cardiomyopathies can be subdivided by a variety of criteria. The 2006 American Heart Association classification divides them into three major groups: (1) *Primary* includes those entities in which the disease is solely or predominantly of the heart; (2) *Secondary* in which heart is involved as a part of a generalized multiorgan disorder. Within each category, some are genetic, others are acquired, and many are idiopathic. A more clinical and functional classification is given in groups (Fig. 11-23 and Table 11-5) as follows:

Dilated cardiomyopathy   Hypertrophic cardiomyopathy   Restrictive cardiomyopathy

Among these, dilated cardiomyopathy is most common (90% of cases), and restrictive cardiomyopathy is least common. There is a spectrum of clinical severity, and each of these three patterns can be caused by idiopathic (Table 11-5). While the recent American Heart Association classification is intellectually appealing, the older clinicopathologic classification since, at present, it is more useful for patient management.

Before we go into further details, some comments are in order about myocarditis. They are included among the cardiomyopathies since there is clinical overlap between some cases of myocarditis and dilated cardiomyopathy. In some cases, dilated cardiomyopathy can be shown to evolve from acute myocarditis. Indeed, since experiments also include myocarditis among cardiomyopathies, we seem to be in good company!

### Dilated Cardiomyopathy

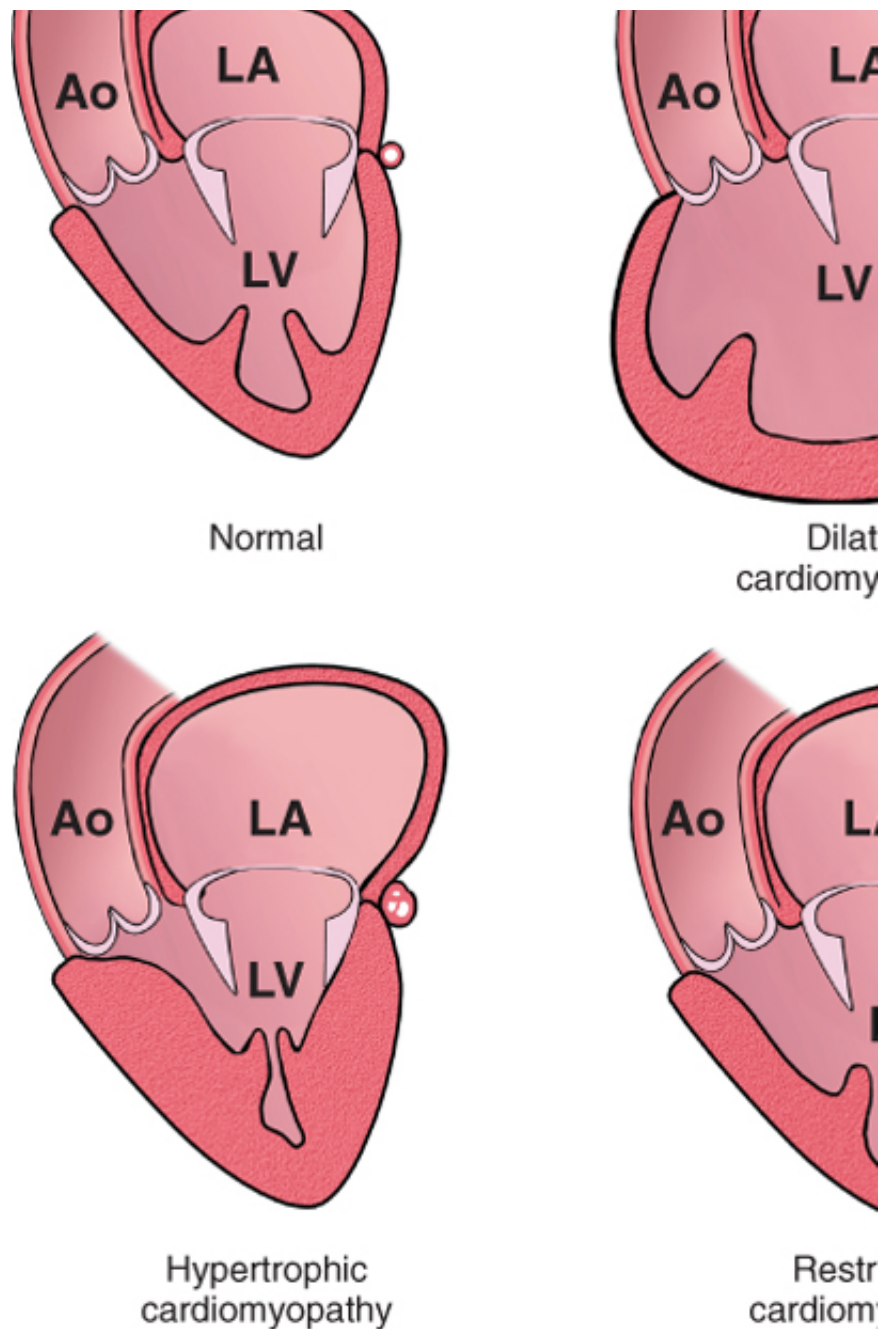
Table 11-5. Cardiomyopathy and Indirect Myocardial Dysfunction: Functional Pattern

Functional Pattern	Left Ventricular Ejection Fraction*	Mechanisms of Heart Failure	Causes	Indirect Effects (Not Exhaustive)
Dilated	<40%	Impairment of contractility (systolic dysfunction)	Idiopathic; alcohol; peripartum; genetic; myocarditis; chronic anemia; doxorubicin (Adriamycin)	Ischemic heart disease; congestive heart failure
Hypertrophic	50% to 80%	Impairment of compliance (diastolic dysfunction)	Genetic; Friedreich ataxia; storage diseases; infants of diabetic mothers	Hypertension; heart failure
Restrictive	45% to 90%	Impairment of compliance (diastolic dysfunction)	Idiopathic; amyloidosis; hemochromatosis; sarcoidosis; radiation-induced fibrosis	Pericardial disease; heart failure

\*Normal,  $\geq 65\%$ .







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Figure 11-23 The three distinctive and predominant clinical-pathologic-functional forms of

Dilated cardiomyopathy (DCM) is characterized by progressive cardiac dilation and *contractile* (sy concurrent hypertrophy. It is sometimes called congestive cardiomyopathy. Approximately 25% to (genetic) basis. Others result from a variety of acquired myocardial insults including toxic exposure and pregnancy-associated changes (see later). In some patients, the cause of DCM is unknown. *Idiopathic dilated cardiomyopathy*. Many in this category are likely to be of genetic origin. Regarding clinicopathologic picture.

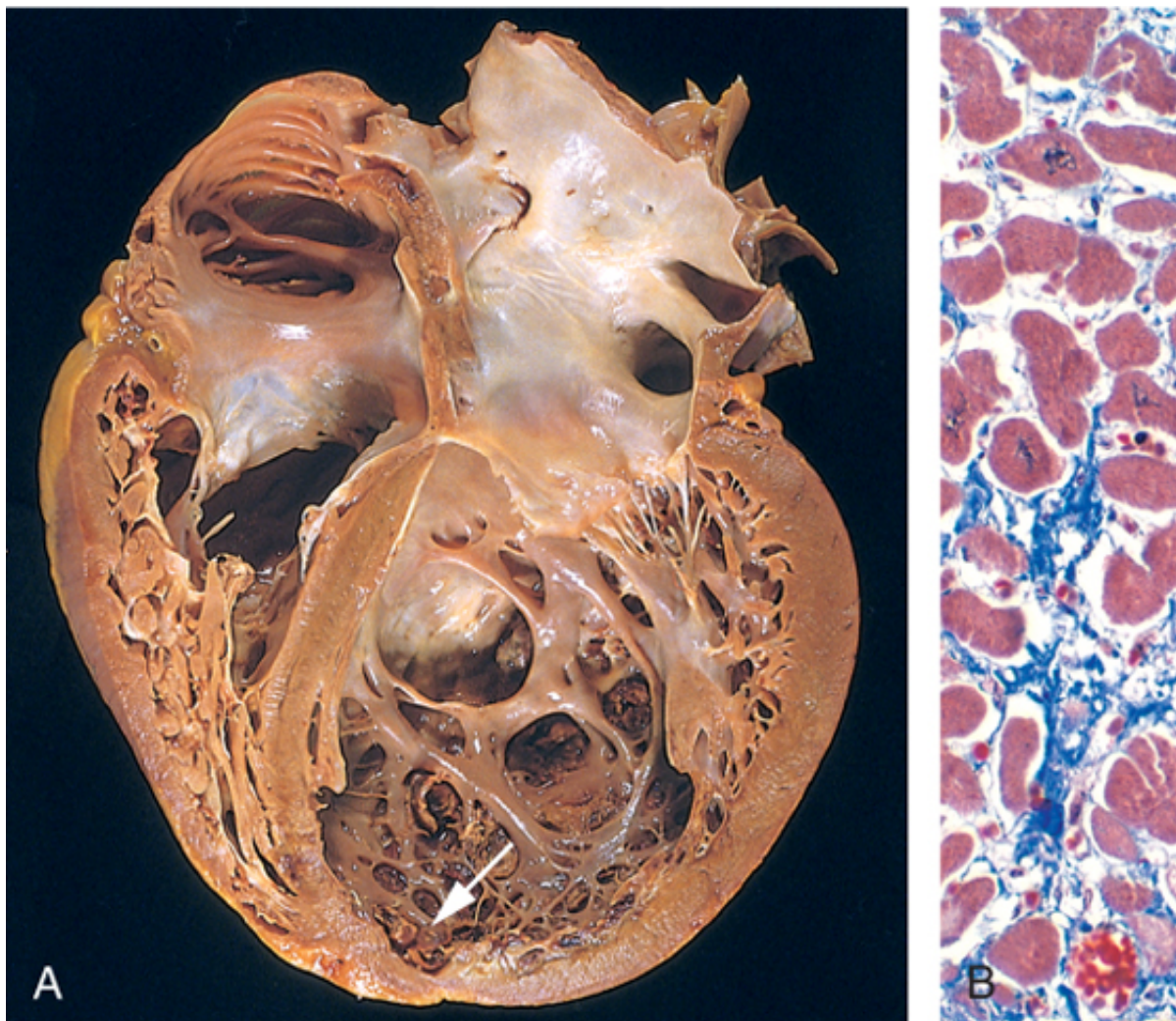
### Morphology

The heart in DCM is characteristically **enlarged** (two to three times its normal weight)

**dilation of all chambers** (Fig. 11-24). Because of the wall thinning that accompanies dilation, the wall thickness may be less than, equal to, or greater than normal. **Mural thrombi** are a common source of thromboemboli. By definition there is no primary valve pathology; consequent regurgitation or insufficiency is a secondary consequence of ventricular chamber dilation. The coronary arteries are free of significant atherosclerotic stenosis.

The histologic abnormalities in DCM are nonspecific. Microscopically most myocytes have **enlarged nuclei**, but many are attenuated, stretched, and irregular. There is variable endocardial fibrosis; scattered scars are also often present, probably marking previous myocardial necrosis caused by reduced perfusion (due to poor contractile function) and increased myocyte hypertrophy. The extent of the changes frequently does not reflect the degree of the patient's prognosis.

### Pathogenesis



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 Figure 11-24 Dilated cardiomyopathy (DCM). **A**, Four-chamber dilatation and hypertrophy are evident. There is a small right ventricle (on the right in this apical four-chamber view). There was no coronary artery disease. **B**, Histology of the myocardium showing hypertrophy and interstitial fibrosis (collagen is highlighted as blue in this Masson's trichrome stain).

When discovered clinically, DCM is frequently at its end stage, and many hearts show only the end-stage changes. As a result the etiology can often only be inferred by the patient's medical history, or it is based on epidemiologic data.

can be grouped into four broad categories:

**Viral.** The nucleic acid "footprints" from coxsackievirus B and other enteroviruses can occur. Moreover, sequential endomyocardial biopsies have documented cases where there is progressive inflammation, simply finding viral transcripts may be sufficient to invoke a myocarditis that is not due to *other toxic exposure*. Alcohol abuse is strongly associated with development of DCM. Alcohol and acetaldehyde have a direct toxic effect on myocardium ([Chapter 8](#)). Moreover, chronic alcoholism, introducing an element of beriberi heart disease ([Chapter 8](#)). Nevertheless, the role of alcohol alone is debated, and no morphologic features serve to distinguish *alcoholic cardiomyopathy*. Nonalcoholic toxic insults include certain chemotherapeutic agents, particularly doxorubicin and its *influences*. Familial forms of DCM account for 25% to 35% of cases; autosomal dominant inheritance, X-linked, autosomal recessive, and mitochondrial inheritances are less common. Most of the defects affect the myocyte cytoskeleton. Although not the most common form, X-linked DCM caused by mutations in the dystrophin gene is well understood. Dystrophin is an intracellular structural protein that plays a critical role in linking the myocyte to the extracellular matrix; indeed, dystrophin is mutated in the most common muscular dystrophy, Duchenne's muscular dystrophy. In some patients with dystrophin gene mutations have DCM as the primary clinical feature. Other forms of DCM include  $\alpha$ -cardiac actin (links the sarcomere with dystrophin), desmin (the principal in myocytes), and the nuclear lamins A and C. Mitochondrial gene deletions and mutations in genes involved in fatty acid beta-oxidation can presumably cause DCM by altering myocardial ATP generation, particularly in gestation or several weeks to months postpartum. The etiology is multifactorial, including volume overload, nutritional deficiency, other metabolic derangement, and/or an immunologic reaction (e.g., hypersensitivity production). Fortunately, approximately half of these patients spontaneously recover normal function.

### *Clinical Features*

DCM can occur at any age, including in childhood, but it most commonly occurs between ages 20 and 50. It is a slowly progressing CHF (e.g., shortness of breath and poor exertional capacity), but patients can remain in a compensated state. The fundamental defect in DCM is ineffective contraction. Hence in end-systolic volume is typically less than 25%. Secondary mitral regurgitation and abnormal cardiac rhythms are common. Thrombi can occur. Fifty percent of patients die within 2 years, and only 25% survive longer than 5 years. In most cases cardiac transplantation is the only definitive treatment.

### **Arrhythmogenic Right Ventricular Cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy is a unique (albeit uncommon) entity with a clinical picture of heart failure and various rhythm disturbances (including SCD). Morphologically the right ventricular wall is replaced by massive fatty infiltration and lesser amounts of fibrosis. Most cases are sporadic, but some are due to gene defects localized to chromosome 14 (autosomal dominant inheritance with variable penetrance). The disease involves desmosomal junctional proteins.

### **Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) (also known as idiopathic hypertrophic subaortic stenosis) is characterized by *hypertrophy, abnormal diastolic filling*, and in a third of cases *ventricular outflow obstruction*. As discussed in [Chapter 11](#), HCM is dynamic, caused by the anterior leaflet of the mitral valve. The heart is thick-walled, heart failure is common, contrast to the flabby, poorly contractile heart in DCM. Systolic function is usually preserved in HCM and therefore shows primary diastolic dysfunction.

#### **Morphology**

The essential gross feature of HCM is massive myocardial hypertrophy without ventricular dilation ([Fig. 11-25A](#)). The classic pattern of HCM involves disproportionate thickening of the ventricular septum and the left ventricle free wall (so-called **asymmetrical septal hypertrophy**); nevertheless, in some cases there is concentric hypertrophy. On longitudinal sectioning, the ventricular cavity is of a triangular to ovoid shape and is compressed into a "banana-like" configuration ([Fig. 11-25A](#)). There is often an endocardial plaque in the left ventricular outflow tract, as well as a thickening of the mitral valve leaflets. Both findings reflect contact of the anterior mitral leaflet with the septum during ventricular contraction.



correlate with functional left ventricular outflow tract obstruction.

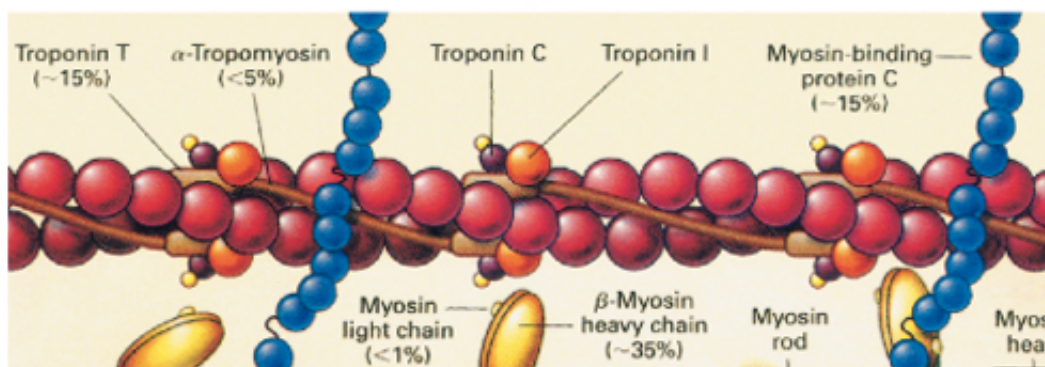
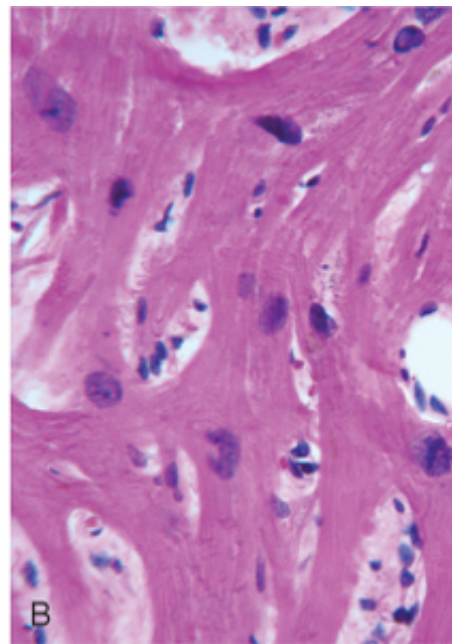
The characteristic histologic features in HCM are **severe myocyte hypertrophy**, **myofiber disarray**, and interstitial and replacement fibrosis (Fig. 11-25B).

### *Pathogenesis*

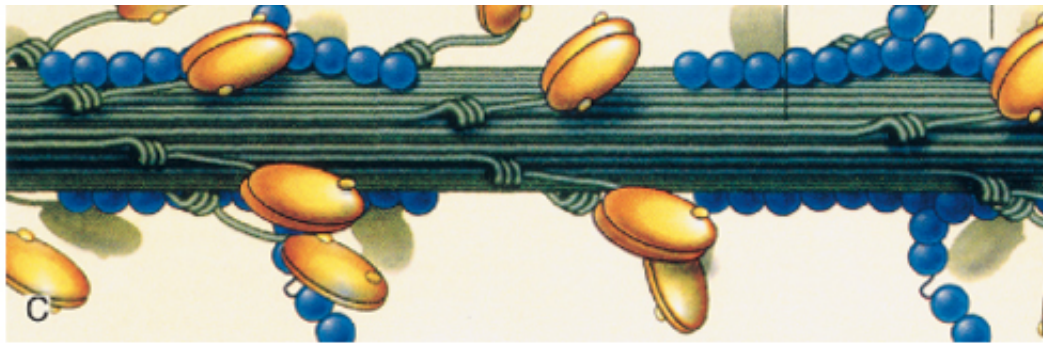
Almost all cases of HCM are caused by missense point mutations in one of several genes encoding the contractile apparatus of striated muscle (Fig. 11-25C). In most cases, the pattern of transmission is autosomal dominant. Greater than 100 causal mutations have been identified in at least 12 sarcomeric genes, with the  $\beta$ -myosin heavy chain being most frequently affected, followed by myosin-binding protein C and troponin T. 80% of all cases of HCM.

Although it is clear that these genetic defects underlie HCM, the sequence of events leading from genotype to phenotype is not fully understood. A current proposal suggests that HCM represents a compensatory change in response to ineffective myocyte contraction triggers exuberant growth factor release with subsequent intense myofiber disarray and fibroblast proliferation (causing interstitial fibrosis).

### *Clinical Features*







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Figure 11-25 Hypertrophic cardiomyopathy (HCM) with asymmetric septal hypertrophy. **A**, The septal muscle bulge into the left ventricle is enlarged. The anterior mitral leaflet has been moved away from the septum to reveal a fibrous endocardial appearance demonstrating disarray, extreme hypertrophy, and characteristic branching of myocytes. **C**, Sarcomere mutations cause defective contraction, hypertrophy, and myocyte disarray in HCM. The frequency of a particular mutation in HCM; most common are mutations in  $\beta$ -myosin heavy chain. Normal contraction of the sarcomere involves binding to troponin C, I, and T, and  $\alpha$ -tropomyosin. Actin stimulates adenosine triphosphatase activity in the myofibrils. Myocyte-binding protein C modulates contraction. (**A**, From Schoen FJ: Interventional and Surgical Cardiology. Philadelphia, WB Saunders, 1989. **C**, From Spirito P, et al.: The management of hypertrophic cardiomyopathy. Copyright © 1997 Massachusetts Medical Society. All rights reserved.)

HCM is characterized by a massively hypertrophied left ventricle that paradoxically provides a pathophysiologic effect is a direct consequence of impaired diastolic filling and overall smaller chamber size. In some patients, dynamic obstruction to the left ventricular outflow by the anterior leaflet of the mitral valve during systole causes a secondary increase in pulmonary venous pressure causing exertional dyspnea, and there is a high risk of massive hypertrophy, high left ventricular pressures, and compromised intramural coronary artery blood flow (ischemia with angina), even in the absence of concomitant coronary artery disease. Major clinical complications include mural thrombus formation, IE of the mitral valve, CHF, arrhythmias, and sudden death. Most patients benefit from medical therapy; occasionally, partial surgical excision of septal muscle is necessary.

### Restrictive Cardiomyopathy

Restrictive cardiomyopathy is characterized by a primary decrease in ventricular compliance, resulting in a stiff ventricle (diastole). The contractile (systolic) function of the left ventricle is usually normal. Restrictive cardiomyopathy can be confused with that of constrictive pericarditis or hypertrophic cardiomyopathy. Restrictive cardiomyopathy is associated with systemic diseases that also happen to affect the myocardium—for example, radiation-induced fibrosis, hemochromatosis, sarcoidosis, or products of inborn errors of metabolism. For each of these causes, see the more complete discussion in the relevant chapters. Genetic factors are less clearly defined in restrictive cardiomyopathy.

#### Morphology

In idiopathic restrictive cardiomyopathy the ventricles are of approximately normal size, and the myocardium is firm. Biventricular dilation is common. Microscopically there is interstitial fibrosis, varying from minimal and patchy to extensive. Restrictive cardiomyopathy of disparate causes may have similar gross morphology. Endomyocardial biopsy can reveal disease-specific features (e.g., amyloid, iron overload, granulomas).

Two other forms of restrictive cardiomyopathy merit brief mention:

**Endomyocardial fibrosis** is principally a disease of children and young adults in Africa and Asia, characterized by dense fibrosis of the ventricular endocardium and subendocardium extending from the apex to the base. The fibrous tissue markedly diminishes the volume and compliance of affected chambers and leads to heart failure. Worldwide, this is the most common form of restrictive cardiomyopathy. **Loeffler endomyocarditis** is typically associated with large mural thrombi; however, Loeffler endomyocarditis is not geographically restricted. It is characterized by peripheral hypereosinophilia; the circulating eosinophils are abnormal, and many are degenerate.

granule contents, especially major basic protein, is speculated to initiate endocardial damage, followed by necrosis and then fibrosis. The release of granule contents followed by necrosis is followed by scarring of the necrotic area.

## Myocarditis

In myocarditis there is inflammation of the myocardium with resulting injury. It is important, however, that inflammation alone is *not* diagnostic of myocarditis; for example, inflammatory infiltrates can also be seen in ischemic injury. *In myocarditis, the inflammatory process is the cause of—rather than a response to—*

### Morphology

During active myocarditis the heart may appear normal or dilated. The ventricular wall may be flabby and often mottled by patchy or diffuse foci of pallor and/or hemorrhage. Macroscopically, active myocarditis shows an interstitial inflammatory infiltrate, with mononuclear cells adjacent to the inflammatory cells (Fig. 11-26).

**Lymphocytic myocarditis** is most common (Fig. 11-26A). If the patient survives the acute phase of myocarditis, the inflammatory lesions either resolve, leaving no residual changes, or are replaced by fibrosis.

**Hypersensitivity myocarditis** has interstitial and perivascular infiltrates composed of mononuclear cells, macrophages, and a high proportion of eosinophils (Fig. 11-26B).

**Giant-cell myocarditis** is a morphologically distinctive entity characterized by wide areas of cellular infiltrates containing multinucleate giant cells (formed by macrophage fusion of lymphocytes, eosinophils, and plasma cells). Giant-cell myocarditis probably represents the spectrum of lymphocytic myocarditis, and there is at least focal—and frequently extensive—myocardial necrosis (Fig. 11-26C). This variant carries a poor prognosis.

**Chagas myocarditis** is distinctive by virtue of the parasitization of scattered myofibers, accompanied by an inflammatory infiltrate of neutrophils, lymphocytes, macrophages, and eosinophils (Fig. 11-26D).

## Pathogenesis

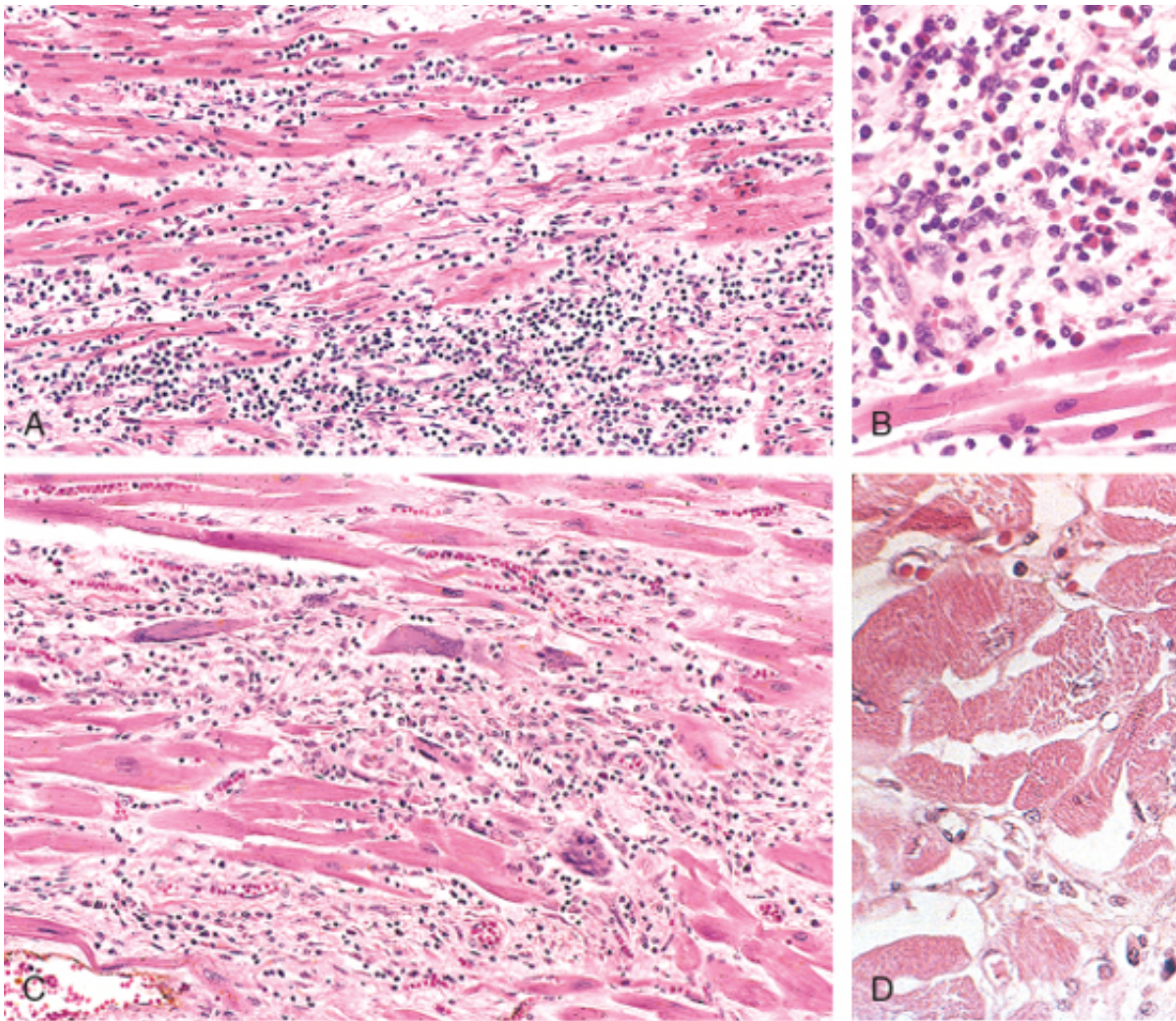
In the United States, viral infections are the most common cause of myocarditis. Coxsackieviruses probably account for most of the cases. Less common agents include cytomegalovirus, human immunodeficiency virus, and other agents (Table 11-6). Although it is often difficult to isolate the offending virus from infected tissue, molecular biology techniques (e.g., polymerase chain reaction) can occasionally point to the culprit. Some viruses can induce cross-reactive antibodies or T lymphocytes. In most cases, however, the injury is caused by virus-infected cells (Chapter 5); this is analogous to the damage inflicted by virus-specific T cells (Chapter 16).

The *nonviral infectious causes of myocarditis* run the entire gamut of the microbial world (Table 11-7), including the agent of Chagas disease. Although uncommon in the northern hemisphere, Chagas disease is endemic in certain areas of South America, and myocardial involvement can be found in 80% of infected individuals during an acute attack; others enter a chronic immune-mediated phase and develop progressive heart failure and arrhythmias 10 to 20 years later. *Toxoplasma gondii* (household cats are the most common vector) can cause myocarditis in immunocompromised hosts. *Trichinosis* is the most common helminthic disease with associated myocarditis.

Myocarditis occurs in approximately 5% of patients with Lyme disease, a systemic illness caused by *Borrelia burgdorferi*. Lyme myocarditis manifests primarily as a self-limited conduction system disease. A first-degree AV block is present in approximately 30% of patients.







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Figure 11-26 Myocarditis. **A**, Lymphocytic myocarditis, with mononuclear inflammatory cell infiltrate and associated characterized by interstitial inflammatory infiltrate composed largely of eosinophils and mononuclear inflammatory cells in large interstitial spaces. This form of myocarditis is associated with drug hypersensitivity. **C**, Giant-cell myocarditis containing lymphocytes and macrophages, extensive loss of muscle, and multinucleated giant cells. **D**, The myocardium with trypanosomes (arrow). There is a surrounding inflammatory reaction and individual

**Table 11-6. Major Causes of Myocarditis**

<b>Infections</b>
Viruses e.g., coxsackievirus, ECHO, influenza, HIV, cytomegalovirus
Chlamydiae e.g., <i>C. psittaci</i>
Rickettsiae e.g., <i>R. typhi</i> , typhus fever
Bacteria e.g., <i>Corynebacterium diphtheriae</i> , <i>Neisseria meningococcus</i> , <i>Borrelia</i> (Lyme disease)
Fungi e.g., <i>Candida</i>
Protozoa e.g., <i>Trypanosoma</i> (Chagas disease), toxoplasmosis
Helminths e.g., trichinosis
<b>Immune-Mediated Reactions</b>
Postviral
Poststreptococcal (rheumatic fever)
Systemic lupus erythematosus

Drug hypersensitivity (e.g., <a href="#">methyldopa</a> <sup>®</sup> , sulfonamides)
Transplant rejection
<b>Unknown</b>
Sarcoidosis
Giant-cell myocarditis

HIV, human immunodeficiency virus.

*Noninfectious causes of myocarditis* include systemic diseases of immune origin, such as lupus and hypersensitivity reactions (*hypersensitivity myocarditis*) can also occur in response to any of a wide variety of agents. In most cases, the disease is benign and only in rare circumstances lead to CHF or sudden death.

### *Clinical Features*

The clinical spectrum of myocarditis is broad. At one end, the disease is asymptomatic and patients at the other end is the precipitous onset of heart failure or arrhythmias, occasionally with sudden death. The various forms of presentation, associated with a variety of symptoms (e.g., fatigue, dyspnea, palpitations), myocarditis can even mimic those of acute MI. Occasionally, over many years, patients can progress to chronic heart failure.

## SUMMARY

### Cardiomyopathy

Cardiomyopathy is a term applied to intrinsic disease of the cardiac muscle; it can be caused by various factors, or it may be idiopathic. There are three general pathophysiologic categories of cardiomyopathy: dilated (90%), hypertrophic, and restrictive (least common). Dilated cardiomyopathy results in systolic (contractile) dysfunction. It may be acquired, for example, by alcohol, toxic exposures (e.g., alcohol), or pregnancy (peripartum). In 25% to 35% of cases, genetic defects in cytoskeletal proteins are causal. Hypertrophic cardiomyopathy results in diastolic dysfunction. The vast majority of cases are due to autosomal dominant mutations encoding the contractile apparatus, in particular  $\beta$ -myosin heavy chain. Restrictive cardiomyopathy results in a stiff, noncompliant myocardium and can be due to depositions (e.g., amyloidosis, hemochromatosis), increased interstitial fibrosis (e.g., caused by irradiation), or scarring. Myocarditis results from muscle injury caused by an inflammatory process, which can be primary or secondary to infections or immune reactions. Coxsackieviruses A and B are the most common causes in the U.S. Clinically, myocarditis may be asymptomatic, give rise to acute heart failure, or progress to dilated cardiomyopathy.



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## PERICARDIAL DISEASE

Diseases of the pericardium include inflammatory conditions and effusions. Isolated pericardial disease is unusual, and pericardial lesions are almost always associated with disease in other portions of the heart or surrounding structures, or are secondary to a systemic disorder.

### Pericarditis

*Primary pericarditis is uncommon;* in most cases it is caused by infection. *Viruses are usually responsible,* although other organisms (e.g., bacteria and fungi) can be involved. Myocarditis can also be present, especially with viral disease.

In most cases pericarditis is secondary to acute MI, cardiac surgery, irradiation to the mediastinum, or processes involving other thoracic structures (e.g., pneumonia or pleuritis). *Uremia* is the most common systemic disorder associated with pericarditis. Less common secondary causes include rheumatic fever, systemic lupus erythematosus, and metastatic malignancies. Pericarditis can (1) cause immediate hemodynamic complications if a significant effusion is present (see below), (2) resolve without significant sequelae, or (3) progress to a chronic fibrosing process.

### Morphology

The appearance of **acute pericarditis** varies slightly depending on its cause. In patients with viral pericarditis or uremia, the exudate is typically **fibrinous**, imparting an irregular (even shaggy) appearance to the pericardial surface (so-called bread-and-butter pericarditis). In acute bacterial pericarditis the exudate is **fibrinopurulent** (suppurative), often with areas of frank pus ([Fig. 11-27](#)); tuberculous pericarditis can show areas of caseation. Pericarditis due to malignancy is often associated with an exuberantly shaggy fibrinous exudate and a bloody effusion; metastases can be grossly evident as irregular excrescences or may be relatively inapparent, especially in the case of leukemia. In most cases, acute fibrinous or fibrinopurulent pericarditis resolves without any sequelae. However, when there is extensive suppuration or caseation, healing can result in fibrosis (**chronic pericarditis**).

The appearance of chronic pericarditis ranges from delicate adhesions to dense, fibrotic scars that obliterate the pericardial space. In extreme cases the heart is so completely encased by dense fibrosis that it cannot expand normally during diastole, so-called **constrictive pericarditis**.

### Clinical Features

Pericarditis classically presents with atypical chest pain, not related to exertion and often worse on reclining, and a prominent friction rub. When associated with significant fluid accumulation, acute pericarditis can cause cardiac tamponade, with declining cardiac output and shock. Chronic constrictive pericarditis produces a combination of right-sided venous distention and low cardiac output, similar to restrictive cardiomyopathy.





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 Figure 11-27 Acute suppurative pericarditis as an extension from a pneumonia. Extensive purulent exudate is evident in this in situ photograph.

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### Pericardial Effusions

Normally, there is about 30 to 50 mL of thin, clear, straw-colored (serous) fluid in the pericardial sac. Pericardial effusions in excess of this amount occur in a number of settings, in addition to the inflammatory states described above. The major types and some of their more common causes include:

**Serous:** CHF, hypoalbuminemia of any cause  
**Serosanguinous:** blunt chest trauma, malignancy, ruptured MI, or aortic dissection  
**Chylous:** mediastinal lymphatic obstruction

The consequences of pericardial effusions depend on the ability of the parietal pericardium to stretch. This, in turn, depends on the amount of fluid and the tempo of its accumulation. Thus, slowly accumulating effusions-even as large as 1000 mL-can be tolerated without clinical manifestation. In contrast, rapidly developing collections of as little as 250 mL (e.g., ruptured MI or ruptured aortic dissection) can restrict diastolic cardiac filling to produce fatal *cardiac tamponade*.



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## CARDIAC TUMORS

### Metastatic Neoplasms

*The most common tumor of the heart is a metastatic tumor; tumor metastases to the heart occur in* Although any malignancy can secondarily involve the heart, certain tumors have a higher predilection. In order of these tumors are carcinoma of the lung, lymphoma, breast cancer, leukemia, melanoma, and sarcoma.

### Primary Neoplasms

*Primary cardiac tumors are uncommon; in addition, most primary cardiac tumors are also (thankfully) benign, with no malignant potential and account for 80% to 90% of all primary heart tumors. In descending order of frequency, the most common cardiac tumors are: myxomas, fibromas, lipomas, papillary fibroelastomas, rhabdomyomas, and angiosarcomas. Only the myxomas and rhabdomyomas will receive any significant attention here.*

#### Myxomas

Myxomas are the most common primary tumor of the adult heart (Fig. 11-28). Roughly 90% are located in the left atrium, accounting for 80% of those.

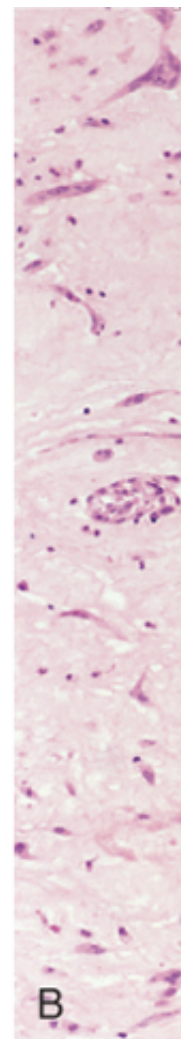
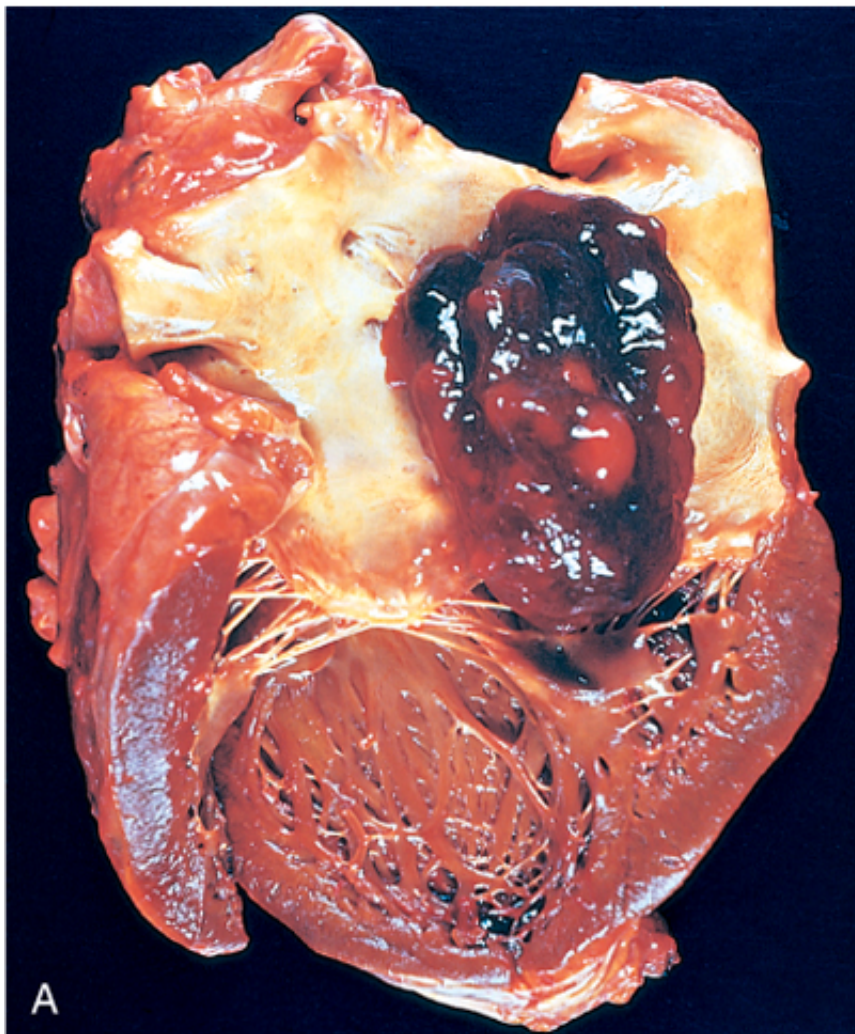




Figure 11-28 Left atrial myxoma. **A**, Gross photograph showing large pedunculated lesion arising from the region of the mitral valve orifice. **B**, Microscopic appearance, with abundant amorphous extracellular matrix in which are scattered myxoma cells (arrowheads) in various groupings, including abnormal vascular formations.

### Morphology

Myxomas are almost always single and are most commonly located at the fossa of the mitral valve. They range from small (<1 cm) to impressive ( $\leq 10$  cm), sessile or pedunculated masses that vary from globular hard masses to soft, translucent, villous lesions with a gelatinous consistency. Pedunculated forms are often sufficiently mobile to swing into the mitral or tricuspid valve causing intermittent obstruction. Sometimes such mobility exerts a "wrecking-ball" effect on the valve leaflets.

Histologically myxomas are composed of stellate, multinucleated myxoma cells with admixed with cells showing endothelial, smooth muscle, and/or fibroblastic differentiation. There is abundant acid mucopolysaccharide ground substance (Fig. 11-28B). Hemorrhage, thrombus, and mononuclear inflammation are also usually present.

### Clinical Features

The major clinical manifestations are due to valvular "ball-valve" obstruction, embolization, or a systemic inflammatory response such as fever and malaise. Constitutional symptoms are probably due to the elaboration of interleukin-6. Echocardiography is the diagnostic modality of choice, and surgical resection is almost always curative.

### Rhabdomyomas

Rhabdomyomas are the most frequent primary tumor of the heart in infants and children; they are usually located in the ventricular wall or protrude into the ventricular chamber. Cardiac rhabdomyomas occur with high frequency in patients with tuberous sclerosis (Chapter 7). Rhabdomyomas are probably better classified as hamartomas or malformations rather than true neoplasms. This classification suggests that these lesions may be caused by defective apoptosis during developmental remodeling.

### Morphology

Rhabdomyomas are generally small, gray-white myocardial masses up to several centimeters in size that protrude into the ventricular chambers. Histologically they have a mixed population of cells, the characteristic of which are large, rounded, or polygonal cells containing numerous vacuoles. These cells are separated by strands of cytoplasm running from the plasma membrane to the more central nucleus. These are the so-called **spider cells**.

### Other Primary Cardiac Tumors

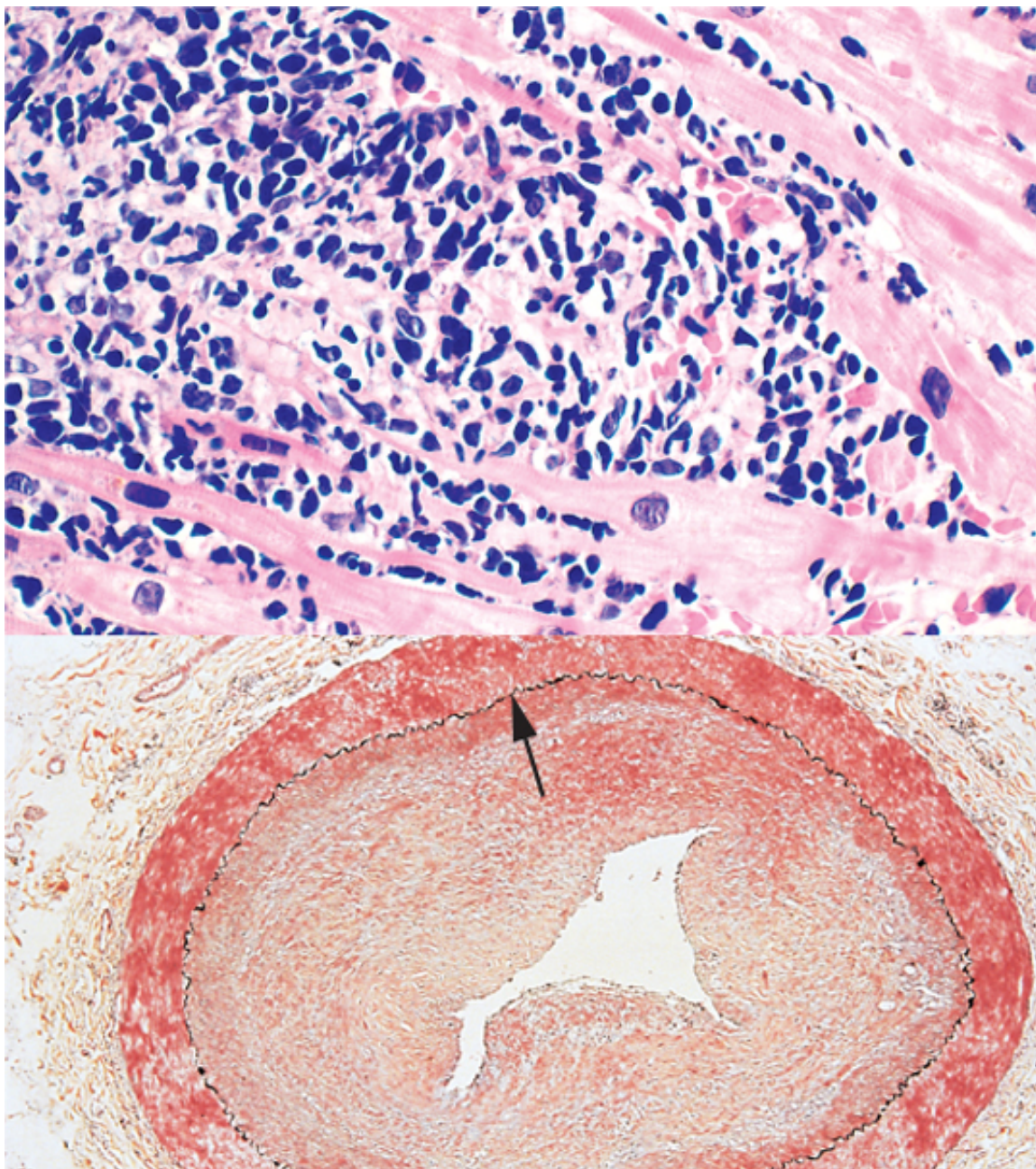
**Lipomas** are localized, poorly encapsulated masses of adipose tissue, which can be asymptomatic or cause obstruction (as with myxomas), or can produce arrhythmias. Lipomas are typically located in the right ventricle or the right atrium. **Papillary fibroelastomas** are curious, usually incidental, lesions that can sometimes obstruct the mitral or aortic valves, forming hairlike projections that grossly resemble sea anemones. Histologically they consist of a core of abundant mucopolysaccharide matrix and laminated elastic fibers, all surrounded by endothelial cells. In some cases, these lesions represent organized thrombi. Cardiac sarcomas are not clinically or morphologically distinctive from their counterparts in other locations.

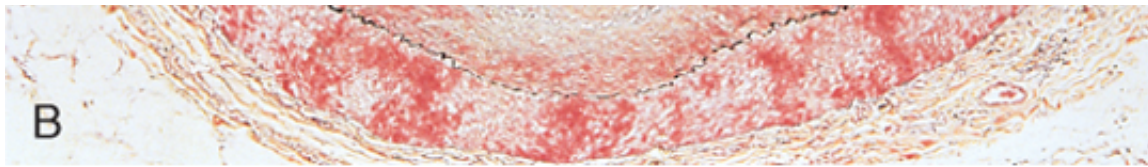




## CARDIAC TRANSPLANTATION

An estimated five million people in the United States have heart failure, and 300,000 die each year as a direct consequence. Cardiac transplantation is increasingly an option for these patients (mostly for IHD and dilated cardiomyopathy), with roughly 2000 performed annually in the U.S. (3000 a year worldwide). A brief look at the numbers suggests that *many* more patients die while on a waiting list (estimated at 50,000 per year) than are successfully transplanted. Indeed, even though the demand for hearts has doubled in the last decade, largely as a result of better ways to support patients in severe failure, the actual supply has dropped.





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 Figure 11-29 Complications of heart transplantation. **A**, Cardiac allograft rejection typified by lymphocytic infiltrate, with associated damage to cardiac myocytes. Note the similarity between rejection and typical viral myocarditis (see Fig. 11-26A). **B**, Graft coronary arteriosclerosis, demonstrating severe diffuse concentric intimal thickening producing critical stenosis. The internal elastic lamina (*arrow*) and media are intact (Movat pentachrome stain, elastin black). (**B**, From Salomon RN, et al.: Human coronary transplantation-associated arteriosclerosis. Evidence for chronic immune reaction to activated graft endothelial cells. Reprinted from Am J Pathol 138:791, 1991 with permission from the American Society for Investigative Pathology.)

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Beyond the issues of supply and demand, the major complications of cardiac transplantation are acute cardiac rejection and graft coronary arteriosclerosis (Fig. 11-29).

*Rejection* is typically diagnosed by endomyocardial biopsy of the transplanted heart; it is characterized by an interstitial lymphocytic inflammation with associated myocyte damage (Fig. 11-29A). The histology is similar to that seen in viral myocarditis (Fig. 11-26A). In both instances, T-cell-mediated killing and local cytokine production can materially compromise cardiac function. When myocardial injury is not extensive, the "rejection episode" can be reversed by immunosuppressive therapy. Advanced rejection can be irreversible and fatal. *Graft coronary arteriosclerosis* (GCA) is the single most important long-term limitation for cardiac transplantation. It is a late, progressive, diffusely stenosing intimal proliferation in the coronary arteries (Fig. 11-29B), leading to ischemic injury. Within 5 years of transplantation, 50% of patients have significant GCA, and virtually all patients have lesions within 10 years. The pathogenesis of GCA involves immunologic responses that induce local production of growth factors that promote intimal smooth muscle cell recruitment and proliferation with extracellular matrix synthesis. GCA is a particularly vexing problem, because it can lead to silent MI (transplant patients have denervated hearts and do not experience angina), progressive CHF, or SCD.

Despite these problems, the outlook for transplanted patients is generally good, with a 1-year survival of 80% and 5-year survivals of more than 60% (compared with 50% and <10%, respectively, in medically managed end-stage heart failure).

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## 12 The Hematopoietic and Lymphoid Systems

JON C. ASTER MD, PhD

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Disorders of the hematopoietic and lymphoid systems encompass a wide range of diseases that are traditionally sorted into disorders that primarily affect red cells, white cells, or the hemostatic system, which includes platelets and clotting factors. The most common *red cell disorders* lead to *anemia*, a state of red cell deficiency. *White cell disorders*, in contrast, are most often caused by excess proliferation, which usually has a neoplastic basis. Hemostatic derangements result in *hemorrhagic diatheses* (bleeding disorders). Finally, splenomegaly, a feature of several hematopoietic diseases, is discussed at the end of the chapter, as are tumors of the thymus.

Although these divisions are useful, in reality the production, function, and destruction of red cells, white cells, and components of the hemostatic system are closely linked, and pathogenic derangements primarily affecting one cell type or component of the system often lead to alterations in others. For example, in certain conditions B lymphocytes make autoantibodies against components of the red cell membrane. The opsonized red cells are recognized and destroyed by phagocytes in the spleen, which becomes enlarged. The increased red cell destruction causes anemia, which in turn drives a compensatory hyperplasia of red cell progenitors in the bone marrow.

Other levels of interplay and complexity stem from the dispersed nature of the lymphohematopoietic system, which is not confined to a single anatomic site. When considering hematopoietic disorders, it is important to remember that both normal and malignant lymphoid and hematopoietic cells "traffic" between various compartments. Hence, a patient who is diagnosed by lymph node biopsy to have a malignant lymphoma may also be found to have neoplastic lymphocytes in the bone marrow and blood. The malignant lymphoid cells in the marrow may suppress hematopoiesis, giving rise to cytopenias, and the further seeding of tumor cells to the liver and spleen may cause organomegaly. Thus, in both benign and malignant hematology disorders, a single underlying abnormality can result in diverse, systemic manifestations.





## RED CELL DISORDERS

Disorders of red cells can result in anemia or, less commonly, polycythemia (i.e., an increase in the number of red cells). *Anemia* is a reduction in the oxygen-transporting capacity of blood, which usually stems from a reduction of the total circulating red cell mass to below-normal amounts.

Anemia can result from excessive bleeding, increased red cell destruction, or decreased red cell production. These mechanisms serve as a basis for classifying anemias (Table 12-1). With the exception of the anemia of chronic renal failure, in which erythropoietin-producing cells in the kidney are lost, the decrease in tissue oxygen tension that attends anemia usually triggers increased erythropoietin production. This drives a compensatory hyperplasia of erythroid precursors in the bone marrow and, in severe anemias, the appearance of extramedullary hematopoiesis within the secondary hematopoietic organs (the spleen, liver, and lymph nodes). In well-nourished individuals who become anemic because of acute bleeding or increased red cell destruction (hemolysis), the compensatory response can increase the regeneration of red cells fivefold to eightfold. The hallmark of increased marrow output is reticulocytosis, the appearance of increased numbers of newly formed red cells (reticulocytes) in the peripheral blood. In contrast, disorders of decreased red cell production (aregenerative anemias) are characterized by reticulocytopenia.

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Another classification of anemias is based on the morphology of red cells, which often correlates with the cause of their deficiency. Specific red cell features that provide etiologic clues include the cell size (normocytic, microcytic, or macrocytic), the degree of hemoglobinization—which is reflected in the color of the cells (normochromic or hypochromic)—and the shape of the cells. These features are judged subjectively by visual inspection of peripheral smears and are also expressed quantitatively through the following indices:

*Mean cell volume* (MCV): the average volume per red cell, expressed in femtoliters (cubic microns)  
*Mean cell hemoglobin* (MCH): the average content (mass) of hemoglobin per red cell, expressed in picograms  
*Mean cell hemoglobin concentration* (MCHC): the average concentration of hemoglobin in a given volume of packed red cells, expressed in grams per deciliter  
*Red cell distribution width* (RDW): the coefficient of variation of red cell volume.

**Table 12-1. Classification of Anemia According to Underlying Mechanism**

<b>Blood Loss</b>
Acute: trauma
Chronic: lesions of gastrointestinal tract, gynecologic disturbances
<b>Increased Destruction (Hemolytic Anemias)</b>
Intrinsic (intracorpuseular) abnormalities
Hereditary
Membrane abnormalities
Membrane skeleton proteins: spherocytosis, elliptocytosis
Membrane lipids: abetalipoproteinemia
Enzyme deficiencies
Glycolytic enzymes: pyruvate kinase, hexokinase

Enzymes of hexose monophosphate shunt: glucose-6-phosphate dehydrogenase, glutathione synthetase
Disorders of hemoglobin synthesis
Deficient globin synthesis: thalassemia syndromes
Structurally abnormal globin synthesis (hemoglobinopathies): sickle cell anemia, unstable hemoglobins
Acquired
Membrane defect: paroxysmal nocturnal hemoglobinuria
Extrinsic (extracorporeal) abnormalities
Antibody mediated
Isohemagglutinins: transfusion reactions, erythroblastosis fetalis (Rh disease of the newborn)
Autoantibodies: idiopathic (primary), drug-associated, systemic lupus erythematosus
Mechanical trauma to red cells
Microangiopathic hemolytic anemias: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
Infections: malaria
<b>Impaired Red Cell Production</b>
Disturbance of proliferation and differentiation of stem cells: aplastic anemia, pure red cell aplasia, anemia of renal failure, anemia of endocrine disorders
Disturbance of proliferation and maturation of erythroblasts
Defective DNA synthesis: deficiency or impaired utilization of vitamin B <sub>12</sub> and folic acid <sub>Rx</sub> (megaloblastic anemias)
Defective hemoglobin synthesis
Deficient heme synthesis: iron deficiency
Deficient globin synthesis: thalassemias
Anemia of renal failure
Unknown or multiple mechanisms: myelodysplastic syndrome, anemia of chronic inflammation, myelophthitic anemias due to marrow infiltrations

In modern clinical laboratories, specialized instruments directly measure or automatically calculate the red cell indices. Adult reference ranges are shown in [Table 12-2](#).

As we will discuss, the clinical consequences of anemia are determined by its severity, speed of onset, and underlying pathogenic mechanism. If the onset is slow, adaptations take place that partially compensate for the deficit in O<sub>2</sub> carrying capacity, such as increases in plasma volume, cardiac output, respiratory rate, and red cell 2,3-diphosphoglycerate levels. These changes can largely mitigate the effects of mild to moderate anemia in otherwise healthy individuals, but are less effective in those with compromised pulmonary or cardiac function. *Pallor*, *fatigue*, and *lassitude* are common to all anemias, and are the primary presenting symptoms of the most common types, such as that caused by iron deficiency. Anemias caused by the premature destruction of red cells in the peripheral blood (*hemolytic anemias*) are associated with *hyperbilirubinemia*, *jaundice*, and *pigment gallstones*. Anemias that stem from *ineffective hematopoiesis* (the premature death of erythroid progenitors in the marrow) are associated with inappropriately high levels of iron absorption from the gut, which can lead to iron overload (*secondary hemochromatosis*) and eventual damage to endocrine organs and the heart. If left untreated, *severe congenital anemias*, such as  $\beta$ -thalassemia major, inevitably result in *growth retardation*, *skeletal abnormalities*, and *cachexia*.

## SUMMARY

### Pathology of Anemias

CAUSES  
 Blood loss (hemorrhage)  
 Increased red cell destruction (hemolysis)  
 Decreased red cell production

MORPHOLOGY Microcytic (iron deficiency, thalassemia) Macrocytic (folate or B<sub>12</sub> deficiency) Normocytic but with abnormal shapes (hereditary spherocytosis, sickle cell disease)

CLINICAL MANIFESTATIONS Acute: shortness of breath, organ failure, shock Chronic:

With hemolysis: skeletal abnormalities because of expansion of marrow; growth retardation; jaundice and gallstones With defective erythropoiesis: iron overload, heart and endocrine failure







## ANEMIA OF BLOOD LOSS: HEMORRHAGE

With acute blood loss, the immediate threat to the patient is hypovolemia (shock) rather than anemia. If the patient survives, hemodilution begins at once and achieves its full effect within 2 to 3 days, unmasking the extent of the red cell loss. *The anemia is normocytic and normochromic.* Recovery from blood loss anemia is enhanced by a rise in the erythropoietin level, which stimulates increased red cell production within several days. The onset of the marrow response is marked by reticulocytosis.

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**Table 12-2. Adult Reference Ranges for Red Blood Cells\***

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.6-17.2	12.0-15.0
Hematocrit (HCT)	%	39-49	33-43
Red cell count	$\times 10^6/\text{mm}^3$	4.3-5.9	3.5-5.0
Reticulocyte count	%	0.5-1.5	0.5-1.5
Mean cell volume (MCV)	fL	76-100	76-100
Mean cell Hb (MCH)	pg	27-33	27-33
Mean cell Hb concentration (MCHC)	g/dL	33-37	33-37
Red cell distribution width (RDW)		11.5-14.5	

\*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used when interpreting a laboratory test.

With chronic blood loss, iron stores are gradually depleted. Iron is essential for hemoglobin synthesis and effective erythropoiesis, and its deficiency thus leads to a chronic anemia of underproduction. Iron deficiency anemia can occur in other clinical settings as well, and it is described later in this chapter along with other anemias of diminished erythropoiesis.





## THE HEMOLYTIC ANEMIAS

Normal red cells have a life span of about 120 days. Anemias that are associated with accelerated red cell destruction are called *hemolytic anemias*. Destruction can be caused by either inherent (intracorporeal) red cell defects (extracorporeal) factors, which are usually acquired. Several examples are listed in [Table 12-1](#).

Before discussing the various disorders individually, we will describe certain general features of hemolytic anemias. They are characterized by (1) an increased rate of red cell destruction, (2) a compensatory increase in erythropoiesis that is often accompanied by reticulocytosis, and (3) the retention by the body of the products of red cell destruction (including iron). Because the iron is conserved, regeneration can keep pace with the hemolysis. Consequently, these anemias are almost invariably associated with *hyperplasia within the marrow* and an *increased reticulocyte count in peripheral blood*. In severe cases, extramedullary hematopoiesis often develops in the spleen, liver, and lymph nodes.

Destruction of red cells can occur within the vascular compartment (intravascular hemolysis) or within the mononuclear phagocyte (reticuloendothelial) system (extravascular hemolysis). *Intravascular hemolysis* can result from mechanical factors (e.g., defective heart valve) or biochemical or physical agents that damage the red cell membrane (e.g., clostridial toxins, or heat). Regardless of cause, hemolysis leads to hemoglobinemia, hemoglobinuria, and the release of heme from the heme pigment to bilirubin can result in unconjugated hyperbilirubinemia and jaundice. Massive hemolysis can lead to acute tubular necrosis ([Chapter 14](#)). *Haptoglobin*, a circulating protein that binds and clears free hemoglobin from the plasma.

*Extravascular hemolysis*, the more common mode of red cell destruction, takes place largely within the mononuclear phagocyte system. The mononuclear phagocyte system removes damaged or immunologically targeted red cells. Alterations of shape are necessary for red cells to successfully navigate the splenic sinusoids, and if this passage is difficult and leads to splenic sequestration, followed by phagocytosis. As will be described, this is an important cause of red cell destruction in a variety of hemolytic anemias. Extravascular hemolysis is associated with hemoglobinuria, but it often produces jaundice and, if long-standing, can lead to the formation of gallstones (cholelithiasis). *Haptoglobin* amounts are always decreased, because some hemoglobin invariably binds to haptoglobin. In all forms of hemolytic anemia there is a reactive hyperplasia of the mononuclear phagocyte system.

In chronic hemolytic anemias, changes in iron metabolism lead to increases in iron absorption from the gut. Because the excretion of excess iron is limited, this often causes iron to accumulate, giving rise to systemic iron overload. In severe cases, secondary hemochromatosis ([Chapter 16](#)).

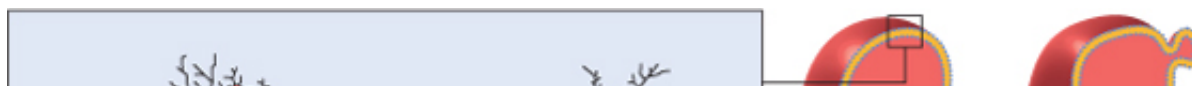
We will now discuss some of the common hemolytic anemias.

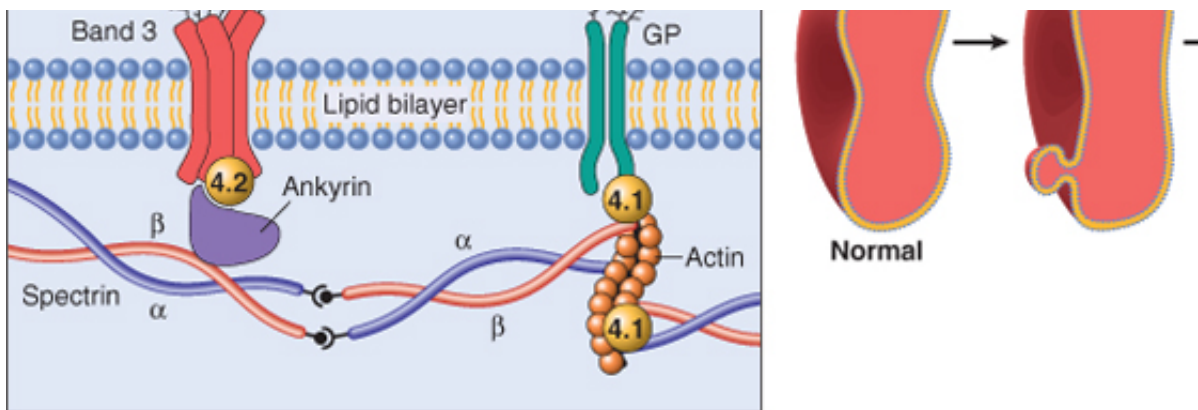
### Hereditary Spherocytosis

This disorder is characterized by an inherited (intrinsic) defect in the red cell membrane that renders the cells rigid and vulnerable to splenic sequestration and destruction. Hereditary spherocytosis (HS) is transmitted as an autosomal dominant trait; approximately 25% of patients have a more severe autosomal recessive form of the disease.

#### Pathogenesis

In HS the primary abnormality resides in one of a group of proteins that form a meshlike supportive skeleton of the red cell membrane ([Fig. 12-1](#)). The major protein in this skeleton is spectrin, a long, flexible heterodimer that is attached to the membrane at two points: through ankyrin and band 4.2 to the intrinsic membrane protein band 3; and through band 4.1 to the extrinsic membrane protein band 2.3. The horizontal spectrin-spectrin and vertical spectrin-intrinsic membrane protein interactions are responsible for the normal shape, strength, and flexibility of the red cell.





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Figure 12-1 The red cell membrane cytoskeleton and the effect of alterations in the cytoskeleton proteins on red cell shape. In the normal biconcave erythrocyte, the membrane cytoskeleton, the normal biconcave erythrocyte loses membrane fragments. To accommodate the spherical shape. Such spherocytic cells are less deformable than normal and are therefore trapped in the splenic cords, where they are destroyed by macrophages.

The common pathogenic feature of all HS mutations is that they weaken the vertical interactions between the membrane proteins. The mutations most frequently involve ankyrin, band 3, and spectrin. In all types of HS the red cells have reduced membrane stability. After release into the periphery, they lose membrane fragments. As a result, the cell volume decreases until the cells become spherical, at which point no further membrane loss is possible.

The spleen plays a major role in the destruction of spherocytes. Red cells must undergo extreme deformation to pass through the splenic sinusoids. The discoid shape of normal red cells allows considerable deformation. In contrast, because of their spheroidal shape and limited deformability, spherocytes are sequestered in the splenic cords and destroyed by macrophages, which are plentiful. *The critical role of the spleen is illustrated by the fact that although the red cell defect and spherocytes persist, the anemia is corrected.*

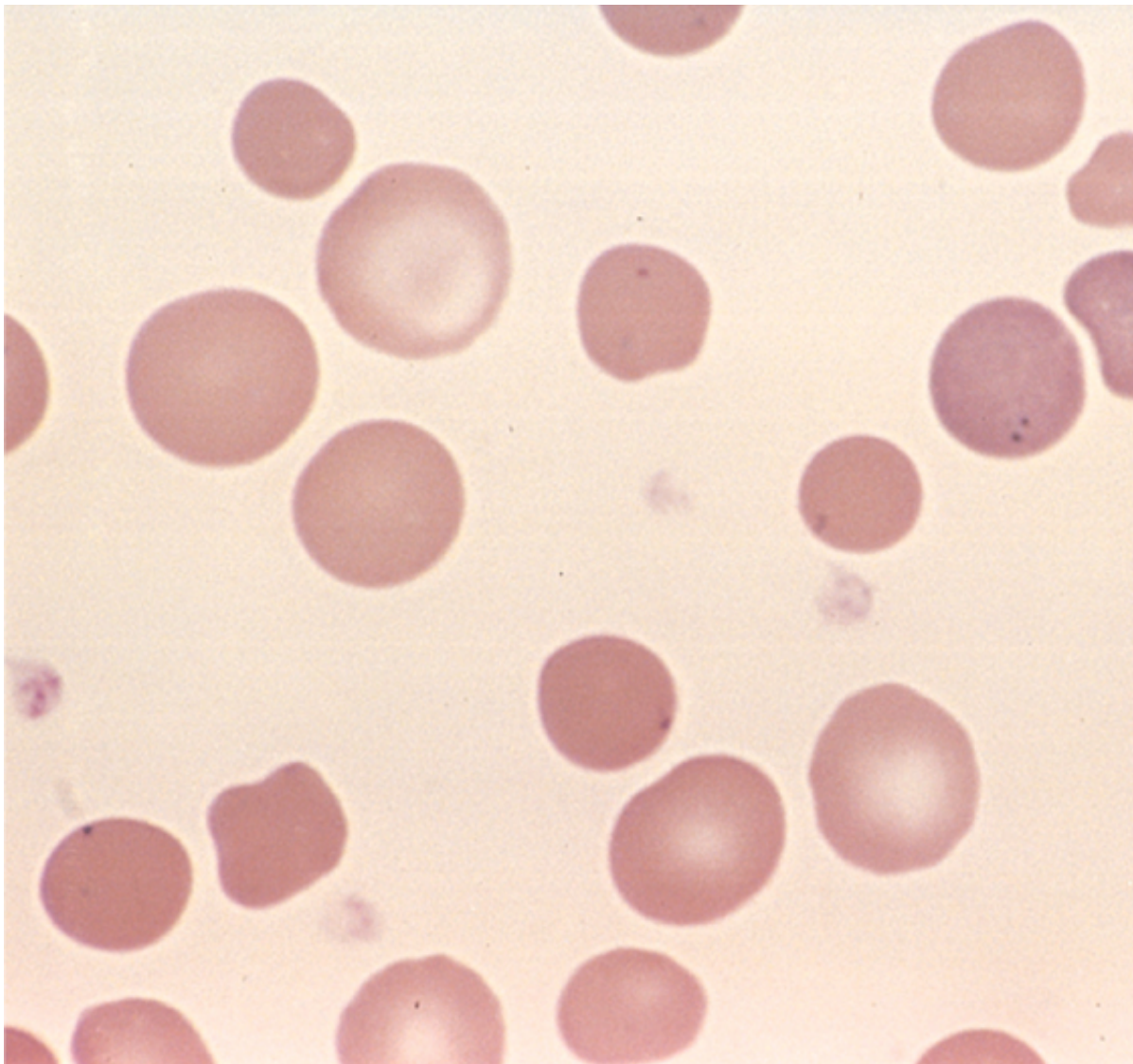
### Morphology

On smears, the red cells lack the central zone of pallor because of their spheroidal shape. Spherocytosis, though distinctive, is not diagnostic; it is seen in other conditions, such as iron deficiency anemia (discussed later), in which there is a loss of cell membrane relative to cell volume. In HS, red cell destruction and resultant anemia lead to a compensatory hyperplasia of marrow and an increase in red cell production, which is marked by peripheral blood reticulocytosis. The spleen is enlarged and more common in HS than in any other form of hemolytic anemia. The spleen is between 500 and 1000 gm and can be even greater. The enlargement results from congestion of Billroth cords and increased numbers of mononuclear phagocytes. Phagocytosis is seen within macrophages lining the sinusoids and, in particular, within the cords. If the spleen is large, there is prominent systemic hemosiderosis. The other general features of hemolytic anemia discussed earlier are also present, including cholelithiasis, which occurs in 40% to 50% of HS.

### Clinical Course

The characteristic clinical features are *anemia*, *splenomegaly*, and *jaundice*. The severity of the anemia ranges from subclinical to profound; most commonly it is moderate in severity. Because of their spheroidal shape and increased membrane fragility when placed in hypotonic salt solutions, a characteristic that is helpful for diagnosis.

The clinical course is often stable but may be punctuated by aplastic crises. Such episodes are characterized by a transient cessation of red cell production. Infection with parvovirus B19, which causes a transient cessation of red cell production for even a few days results in a rapid worsening of the anemia. In some patients need blood transfusions until the infection clears.



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Figure 12-2 Hereditary spherocytosis (peripheral smear). Note the anisocytosis and several dark-appearing spherocytes (small dark nuclear remnants) are also present in the red cells. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Medical School, Dallas, Texas.)

There is no specific treatment for HS. Splenectomy is beneficial for those who are symptomatic, but the spleen is not removed. The benefits of splenectomy must be weighed against the risk of increase in infections in children.

### Sickle Cell Anemia

The hemoglobinopathies are a group of hereditary disorders that are defined by the presence of more than 300 variant hemoglobins that have been discovered, one-third are associated with significant clinical consequences. The most prototypical (and most prevalent) hemoglobinopathy is caused by a mutation in the  $\beta$ -globin chain (HbS). The disease associated with HbS, sickle cell anemia, is discussed here; other hemoglobinopathies are discussed in the next section.

HbS, like 90% of other abnormal hemoglobins, results from a single amino acid substitution in the  $\beta$ -globin chain. As may be recalled, the normal hemoglobin molecule is a tetramer composed of two pairs of similar chains. On average, the normal adult hemoglobin is composed of 97% HbA<sub>1</sub> ( $\alpha_2\beta_2$ ) and 1% fetal Hb (HbF,  $\alpha_2\gamma_2$ ). Substitution of valine for glutamic acid at the sixth



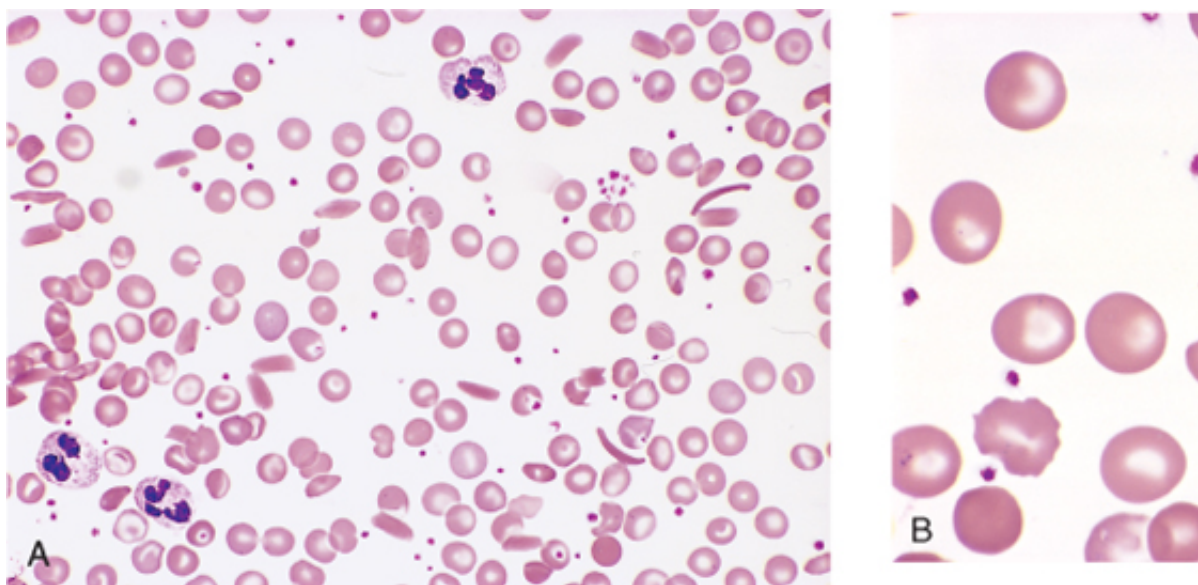
5% Hb<sub>2</sub> (α<sub>2</sub>β<sub>2</sub>), and 1% total Hb (α<sub>1</sub>β<sub>1</sub>, α<sub>2</sub>β<sub>2</sub>). Substitution of valine for glutamic acid at the sixth position of the β chain in HbS causes the amino acid sequence of the β chain to be Val-His-Phe-Tyr-Ser-<sup>6</sup>Pro-Glu-Glu-Glu. In homozygotes all HbA is replaced by HbS, whereas in heterozygotes only about half is replaced.

### Incidence

Approximately 8% of American blacks are heterozygous for HbS. In parts of Africa where malaria approaches 30%, as a result of a small but significant protective effect of HbS against *Plasmodium falciparum*, sickle cell anemia affects approximately one of every 600 blacks, and worldwide, sickle cell anemia affects approximately one of every 5,000 people. Sickle cell anemia is a hemolytic anemia.

### Etiology and Pathogenesis

Upon deoxygenation, HbS molecules undergo polymerization, a process also referred to as *gelation*. The polymers distort the red cell, which assumes an elongated crescentic, or sickle, shape (Fig. 12-3). Sickling occurs during deoxygenation; however, membrane damage occurs with each episode of sickling, and eventually potassium and water, and become irreversibly sickled.

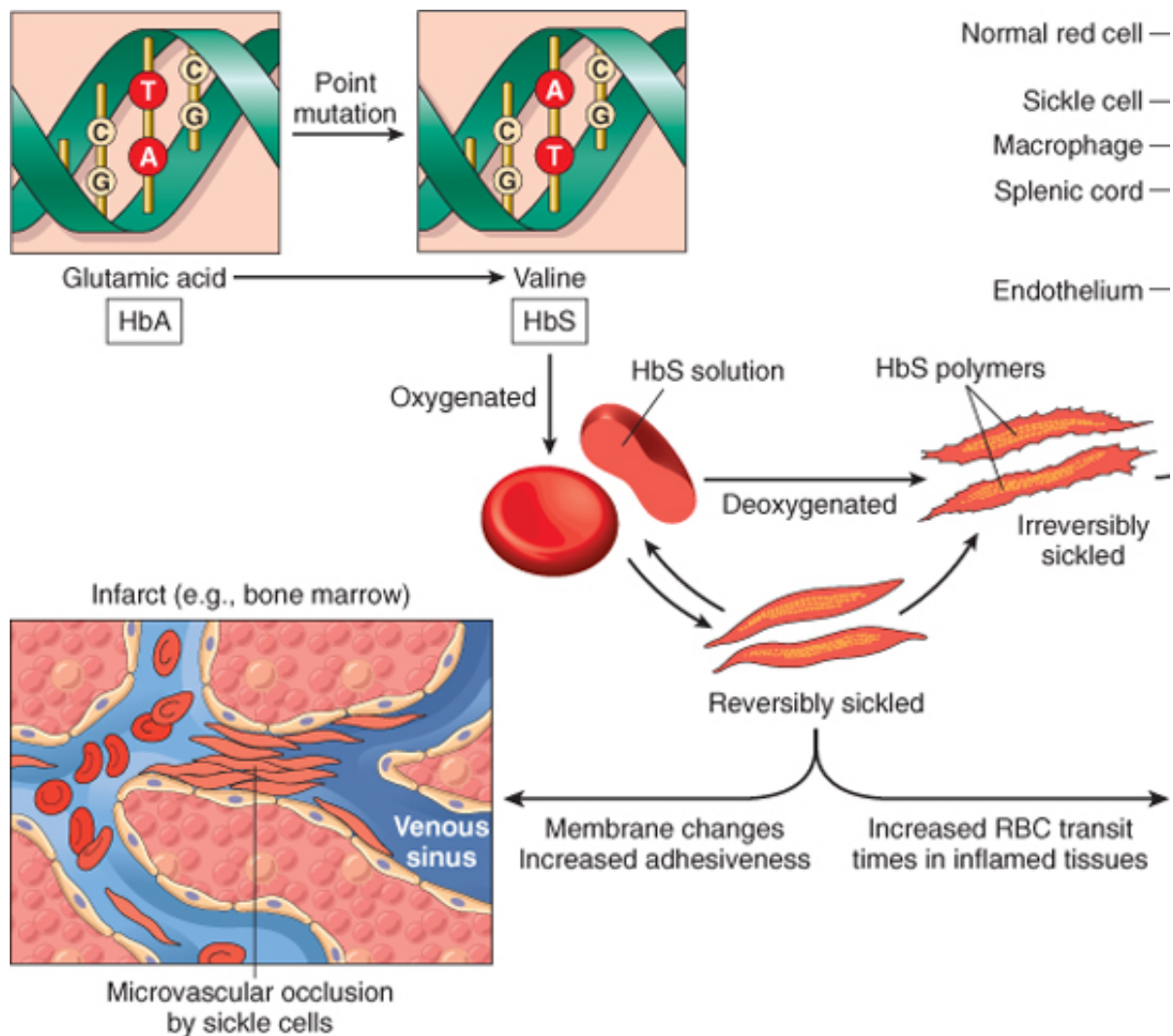


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Figure 12-3 Peripheral blood smear from a patient with sickle cell anemia. A, Low magnification shows sickle cells. B, Higher magnification shows an irreversibly sickled cell in the center. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Many variables influence sickling of red cells in vivo. The three most important ones are as follows:

**The presence of hemoglobins other than HbS.** In heterozygotes approximately 40% of HbA interacts only weakly with deoxygenated HbS. The presence of HbA slows the rate of polymerization. Cells of heterozygotes have little tendency to sickle in vivo. Such individuals are said to have sickle cell trait. The presence of a mutant β-globin, is fairly common. The carrier rate for HbC in American blacks is about 2.3%. HbC, like HbS, is a hemoglobin with a valine substitution at the sixth position of the β chain. Newborns are double heterozygotes because they have inherited HbS from one parent and HbC from the other. HbC has a greater tendency to aggregate with HbS than does HbA, and those with HbS and HbC (called *HbSC*) have a milder form of sickle cell anemia. HbF interacts more weakly with HbS, and therefore newborns with sickle cell anemia do not sickle until about 6 months old, when the HbF falls to adult levels. **The concentration of HbS in the cell.** The rate of polymerization of HbS to form the insoluble polymers that create sickle cells is strongly dependent on the concentration of HbS. An increase in the Hb concentration, greatly facilitates sickling and can trigger occlusion of small blood vessels. The coexistence of α-thalassemia (described later) reduces the Hb concentration and therefore the rate of sickling. **Exposure to low oxygen tension.** Normal transit times for red cells passing through capillaries are usually too short for aggregation of deoxygenated HbS to occur. Hence, sickling is confined to microvascular beds.

aggregation of deoxygenated HbS to occur. Hence, sickling is confined to microvascular beds, normally the case in the spleen and the bone marrow, which are prominently affected by sickle cell anemia. It has been suggested that particularly important pathogenic roles are played by two factors: adhesion. As you will recall, blood flow in inflamed tissues is slowed, as a result of the adhesion of activated endothelium and the exudation of fluid through leaky vessels. This prolongs the residence time of sickle cells, making sickling more likely. Sick red cells also have a greater tendency than normal red cells to adhere to each other apparently because membrane damage makes them sticky. In fact, the adhesion of sickle cells to endothelium correlates with clinical severity, presumably because this "stickiness" reflects a greater risk of thrombosis in vivo.



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Figure 12-4 Pathophysiology and morphologic consequences of sickle cell

Two major consequences stem from the sickling of red cells (Fig. 12-4). First, repeated episodes of damage and dehydration of red cells, which become rigid and irreversibly sickled. These dysfunctional cells are removed by mononuclear phagocyte cells, producing a chronic extravascular hemolytic anemia. In sickle cell anemia, the average lifespan of red cells is only 20 days (one-sixth of normal). Second, the sickling of red cells leads to microvascular obstructions, which result in ischemic tissue damage and pain crises. Vaso-occlusion is caused by irreversibly sickled cells and therefore appears to result from factors, such as infection, inflammation, and the sickling of reversibly sickled cells.

### **morphology**

The anatomic alterations in sickle cell anemia stem from the following three aspects: (1) severe chronic hemolytic anemia; (2) the increased breakdown of heme pigments, bilirubin; and (3) the microvascular obstruction, which provokes tissue ischemia and infarctions. Both the anemia and the vascular stasis lead to fatty changes in the heart, liver, and spleen. The bone marrow shows compensatory hyperplasia of erythroid progenitors. The burgeoning resorption and secondary new bone formation, resulting in prominent cheekbones resembling a "crew-cut" in roentgenograms. Extramedullary hematopoiesis can also occur in the spleen and liver.

In children there is moderate **splenomegaly** (splenic weight as great as 500 gm) of the red pulp, which is stuffed with sickled red cells. However, the chronic splenic enlargement leads to progressive hypoxic tissue damage, which eventually reduces the spleen to a functional fibrous tissue. This process, referred to as **autosplenectomy**, is complete by adulthood.

**Vascular congestion, thrombosis, and infarction** can affect any organ, including the retina, brain, lung, and skin. The bone marrow is particularly prone to ischemia, because of sluggish blood flow and high rate of metabolism. Priapism, another common problem, is caused by fibrosis and eventual erectile dysfunction. As with the other hemolytic anemias, **hepatic gallstones** are common.

### *Clinical Course*

Homozygous sickle cell disease usually becomes apparent after the sixth month of life, since HbF is low; anemia is severe; most patients have hematocrit values of 18% to 30% (normal range, 35%-45%) with marked reticulocytosis and hyperbilirubinemia. From the time of onset, the process runs an unrelenting course with periodic crises. The most serious of these are the *vaso-occlusive*, or *pain, crises*. Pain crises can involve the bone marrow, where they often progress to infarction and necrosis.

A feared complication is the *acute chest syndrome*, which can be triggered by pulmonary infection and secondarily involve the lung. The blood flow in the inflamed, ischemic lung becomes sluggish and hypoxic pulmonary beds. This exacerbates the underlying pulmonary dysfunction, creating a vicious cycle of systemic hypoxemia, sickling, and vaso-occlusion. Another major complication is *central nervous system infarction* in the setting of the acute chest syndrome. Although virtually any organ can be damaged by ischemia, *the acute chest syndrome and stroke are the two leading causes of ischemia-related death*.

A second acute event, the *aplastic crisis*, represents a sudden but usually temporary cessation of erythropoiesis. These are usually triggered by parvovirus infection of erythroblasts, and, while severe, are usually self-limiting.

In addition to these crises, patients with sickle cell disease are prone to *infections*. Both children and adults are functionally asplenic, making them susceptible to infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae*. "hyposplenism" is also a factor. In the earlier childhood phase of splenic enlargement, congestion apparently interferes with bacterial sequestration and killing; hence, even children with enlarged spleens are at risk. Defects in the alternative complement pathway that impair the opsonization of encapsulated bacteria are not entirely clear, but patients with sickle cell disease are particularly predisposed to *Salmonella* infections.

In full-blown sickle cell disease, at least some irreversibly sickled red cells can be seen on a peripheral smear. Sickling can be induced in vitro by exposing cells to marked hypoxia. Ultimately, the diagnosis is confirmed by demonstration of HbS. Prenatal diagnosis of sickle cell anemia can be performed by analyzing the amniocentesis or biopsy of chorionic villi ([Chapter 7](#)).

The clinical course of patients with sickle cell anemia is highly variable. As a result of improved medical care, a number of patients are surviving into adulthood and producing offspring. Of particular importance is the need to prevent pneumococcal infections. Approximately 50% of patients survive beyond the fifth decade. Symptoms rarely and only under extreme conditions, such as following vigorous exertion at high altitudes.

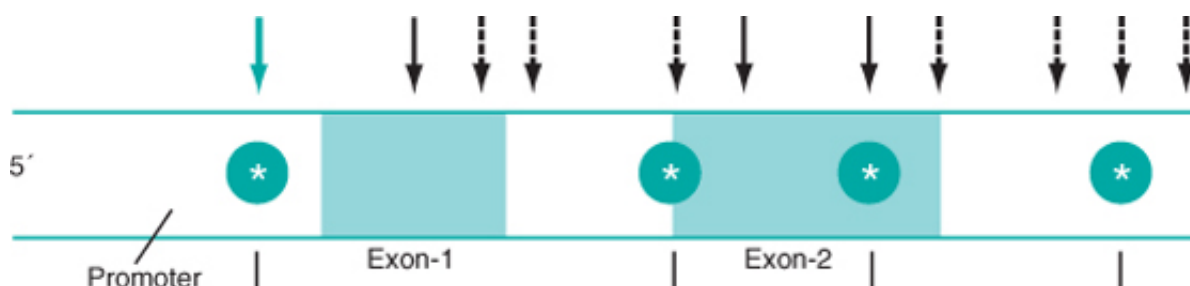
## Thalassemia

## Molecular Pathogenesis

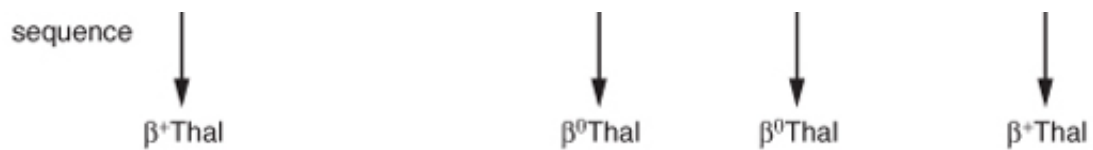
A diverse collection of molecular defects underlies the thalassemias, which are inherited as autosomal recessive disorders. Adult hemoglobin, or HbA, is a tetramer composed of two  $\alpha$  chains and two  $\beta$  chains. The  $\alpha$  chains are encoded by a single  $\alpha$ -globin gene, which lies in tandem on chromosome 11, while the  $\beta$  chains are encoded by a single  $\beta$ -globin gene on chromosome 5. Mutations that cause thalassemia are particularly common among Mediterranean, African, and Asian populations, with the prevalence widely depending on the specific combination of alleles that are inherited by the patient (Table 12.1).

Clinical Nomenclature Genotype		Disease	Molecular Gene
<b>β-Thalassemias</b>			
Thalassemia major	Homozygous or compound heterozygous (β <sup>0</sup> /β <sup>0</sup> , β <sup>0</sup> /β <sup>+</sup> , or β <sup>+</sup> /β <sup>+</sup> )	Severe, requires blood transfusions regularly	Defects in transcription of β-globin mRNA, resulting in no β-globin
β-thalassemia trait	β/β <sup>+</sup> or β/β <sup>0</sup>	Asymptomatic, with mild microcytic anemia, or microcytosis without anemia	
<b>α-Thalassemias</b>			
Hydrops fetalis	-/-	Fatal in utero	Gene deletions spanning α-globin gene
HbH disease	-/-α	Moderately severe anemia	
α-thalassemia trait	-/αα(Asian) or -α/-α(black African)	Similar to β-thalassemia trait	
Silent carrier	-α/αα	Asymptomatic, normal red cells	

The  $\beta$ -globin mutations associated with  $\beta$ -thalassemia fall into two categories: (1)  $\beta^0$ , in which no  $\beta$ -globin is produced, and (2)  $\beta^+$ , in which there is reduced (but detectable)  $\beta$ -globin synthesis. Sequencing of  $\beta$ -thalassemia genes has identified many responsible mutations, the majority of which consist of single-base changes. Individuals inheriting one  $\beta^0$  allele have *thalassemia major*, which is severely symptomatic. Individuals inheriting one  $\beta^+$  allele have *thalassemia minor* or *thalassemia trait*, which is asymptomatic or mildly symptomatic. Most individuals inheriting two  $\beta^+$  alleles have *thalassemia intermedia*; occasionally, individuals inheriting two  $\beta^+$  alleles have a milder disease termed *thalassemia minor*.  $\alpha$ -thalassemias, described later, *gene deletions rarely underlie  $\beta$ -thalassemias* (Table 12-3).



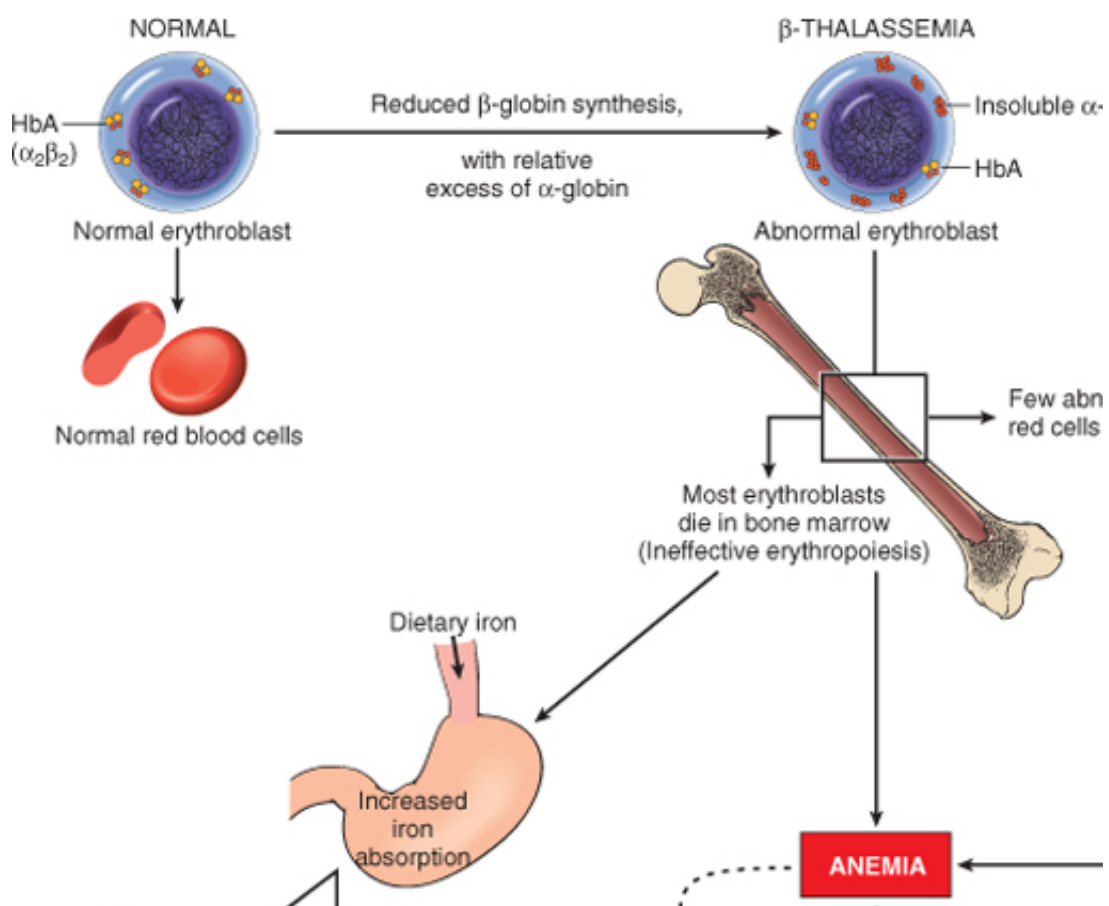


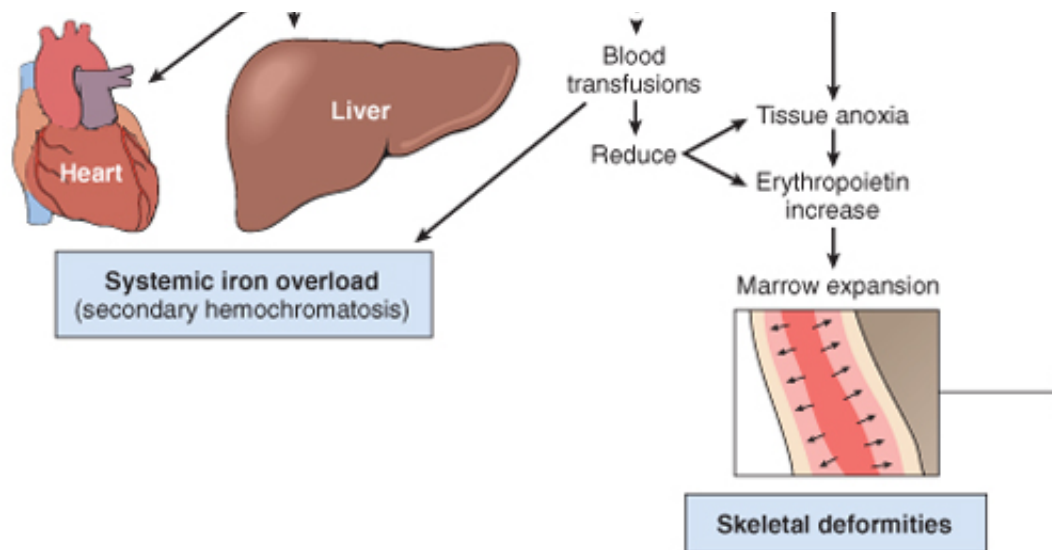


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 Figure 12-5 The  $\beta$ -globin gene and some sites at which point mutations giving rise to  $\beta$ -thalassemia have been located. (Modified from Wyngaarden JB, Smith LH 19th ed. Philadelphia, WB Saunders, 1992.)

Most of the mutations in  $\beta$ -thalassemia fall into one of three molecular subtypes (Fig. 12-5):

The promoter region controls the initiation and rate of transcription. Some mutations lie within the promoter region, leading to reduced globin gene transcription. Because some  $\beta$ -globin is synthesized, such alleles are designated  $\beta^+$ . Sequences that are usually associated with more serious consequences. For example, in some of the exons leads to the formation of a termination, or "stop" codon, which interrupts transcription (mRNA) and completely prevents the synthesis of  $\beta$ -globin. Such alleles are designated  $\beta^0$ . *Processing of the mRNA is the most common cause of  $\beta$ -thalassemia.* Most of these affect introns, but the mutation alters the normal splice junctions, splicing does not occur, and all of the mRNA is degraded within the nucleus, and no  $\beta$ -globin is made. However, some mutations affect a normal intron-exon splice junction. These mutations create new sites that are substrates for abnormal splicing. Because normal splice sites remain intact, normal  $\beta$ -globin mRNA is decreased but not absent. Thus, depending on their precise location, they create either  $\beta^0$  or  $\beta^+$  alleles.





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 Figure 12-6 Pathogenesis of  $\beta$ -thalassemia major. Note that aggregates of excess  $\alpha$ -globin are not visible on routine hand, correct the anemia and reduce stimulus for erythropoietin secretion and deformities induced by marrow expansion iron overload.

Two conditions contribute to the pathogenesis of the anemia in  $\beta$ -thalassemia. The reduced synthesis of  $\beta$ -globin, so that the MCHC is low, and the cells appear *hypochromic* and *microcytic*. Even more results from the unbalanced rates of  $\beta$ -globin and  $\alpha$ -globin chain synthesis. Unpaired  $\alpha$  chains form within the red cells and cause membrane damage that is severe enough to provoke extravascular hemolysis. The bone marrow is also susceptible to damage through the same mechanism, which in severe cases leads to the majority of erythroid progenitors before their maturation into red cells. This intramedullary destruction (*erythrophoresis*) has another untoward effect: it is associated with an inappropriate increase in the rate of erythropoiesis, which leads to iron overload.

#### $\alpha$ -Thalassemia

The molecular basis of  $\alpha$ -thalassemia is quite different from that of  $\beta$ -thalassemia. Most of the  $\alpha$ -thalassemias involve the deletion of one or more of the  $\alpha$ -globin gene loci. The severity of the disease that results from these deletions depends on the number of  $\alpha$ -globin genes that are missing (see Table 12-3). For example, the loss of a single  $\alpha$ -globin gene results in a carrier state, whereas the deletion of all four  $\alpha$ -globin genes is associated with fetal death in utero. With loss of three  $\alpha$ -globin genes there is a relative excess of  $\beta$ -globin chains.  $\beta$ -globin (or  $\gamma$ -globin chains early in life) forms relatively stable  $\beta_4$  and  $\gamma_4$  tetramers known as HbH and Hb Bart. These tetramers cause less membrane damage than do free  $\alpha$ -globin chains. Therefore, the hemolytic anemia and ineffective erythropoiesis in  $\alpha$ -thalassemia are less severe than in  $\beta$ -thalassemia. Unfortunately, both HbH and Hb Bart have an abnormally high oxygen affinity, which is ineffective at delivering oxygen to the tissues.

#### Morphology

Only the morphologic changes in  $\beta$ -thalassemia, which is more common in the United States, are described. In  $\beta$ -thalassemia minor the abnormalities are confined to the peripheral blood smear. The red blood cells appear small (microcytic), pale (hypochromic), and regular in shape. Target cells are a characteristic feature that results from the relatively large surface area-to-volume ratio, which leads to central pallor. In smears from patients with  $\beta$ -thalassemia major the morphologic abnormalities are much more pronounced, and there is marked poikilocytosis, anisocytosis, and reticulocytosis. Nucleated red cells (normoblasts) are also seen, which reflect the increased erythropoietic drive.

The anatomic changes in  $\beta$ -thalassemia major are similar to those seen in other forms of severe anemia, but more extreme in degree. The combination of ineffective erythropoiesis and hemolysis results in severe iron overload.

hyperplasia of erythroid progenitors, with a shift toward early forms. The expanded population may completely fill the intramedullary space of the skeleton, invade the bony cortex, and produce **skeletal deformities**. The extramedullary hematopoiesis and the hyperplastic macrophages result in prominent splenomegaly, **hepatomegaly**, and **lymphadenopathy**. Erythropoietic precursors consume nutrients and produce growth retardation and a clinical picture reminiscent of that seen in cancer patients. Unless steps are taken to prevent iron overload, **severe hemosiderosis** develops (see Fig. 12-6).

### *Clinical Course*

$\beta$ -thalassemia major manifests itself postnatally as HbF synthesis diminishes. Affected children fail to thrive and are retarded from shortly after birth. They are sustained only by repeated blood transfusions, which in turn produce skeletal deformities associated with excessive erythropoiesis. With transfusions alone survival is prolonged but gradually systemic iron overload develops. The combination of iron present in transfused red cells and iron from the gut leads inevitably to iron overload. The latter stems from inappropriately low levels of hepcidin, a hormone that regulates iron uptake that is "underexpressed" in conditions (such as  $\beta$ -thalassemia major) that are associated with increased iron absorption. Unless patients are treated aggressively with iron chelators, cardiac failure from secondary hemochromatosis causes death in the second or third decade of life. When feasible, bone marrow transplantation at birth can be curative.

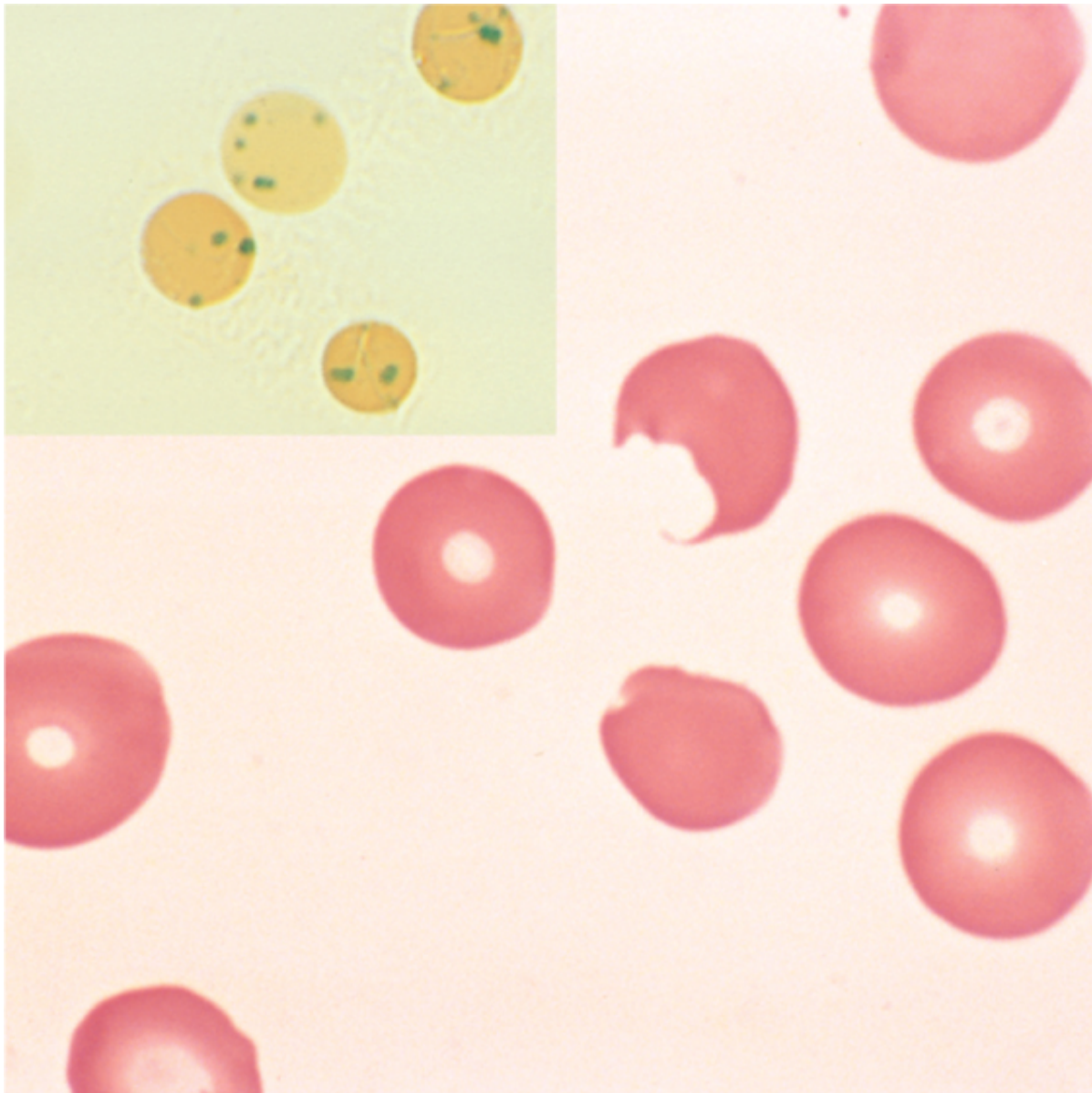
In  $\beta$ -thalassemia minor there is usually only a mild microcytic hypochromic anemia; generally, the clinical picture is asymptomatic. Iron deficiency anemia is associated with a similar red cell appearance and must be distinguished from the thalassemias. The diagnosis of  $\beta$ -thalassemia minor is made by Hb electrophoresis: in  $\beta$ -thalassemia minor, the level of HbA<sub>2</sub> ( $\alpha_2\beta_2$ ) is increased. The diagnosis of  $\beta$ -thalassemia major can generally be made by peripheral blood shows a severe microcytic hypochromic anemia, with marked variation in cell size and shape. The reticulocyte count is increased. Hb electrophoresis shows profound reduction or absence of HbA and increased HbF and HbA<sub>2</sub>. Prenatal diagnosis of both forms of thalassemia can be made by DNA analysis.

HbH disease (caused by deletion of three  $\alpha$ -globin genes) is not as severe as  $\beta$ -thalassemia major. Erythropoiesis is not as imbalanced and hematopoiesis is effective. Anemia is moderately severe, but patients usually do not develop iron overload that is so common in  $\beta$ -thalassemia major is rarely seen.  $\alpha$ -Thalassemia trait (caused by deletion of two  $\alpha$ -globin genes) is often an asymptomatic condition associated with microcytic red cells and mild anemia.

### **Glucose-6-Phosphate Dehydrogenase Deficiency**

The red cell is vulnerable to injury by endogenous and exogenous oxidants, which are normally inactivated by glutathione (GSH). Abnormalities affecting the enzymes that are required for GSH production reduce the ability of red cells to resist oxidative injury and lead to hemolytic anemias. The prototype (and most prevalent) of these anemias is glucose-6-phosphate dehydrogenase (G6PD) deficiency. The G6PD gene is on the X chromosome. More than 200 variants have been identified, but only a few are associated with disease. One of the most important is the G6PD A<sup>-</sup> variant, which is found in 10% of black males in the United States. G6PD A<sup>-</sup> has normal enzymatic activity but a decreased capacity for protein synthesis; older G6PD A<sup>-</sup> red cells become progressively deficient in enzyme activity and are more susceptible to oxidative stress.

G6PD deficiency produces no symptoms until the patient is exposed to an environmental factor (ranging from drugs to infections) that results in increased oxidant stress. The drugs incriminated include antimalarials (e.g., chloroquine, primaquine, phenacetin, aspirin<sup>®</sup> (in large doses), and vitamin K derivatives. More commonly, episodes of hemolysis are induced by infections, which induce phagocytes to produce free radicals as part of the normal host response. These free radicals produce hydrogen peroxide that are sopped up by GSH, which is converted to oxidized glutathione in the process. In G6PD-deficient cells, hydrogen peroxide is free to "attack" other red cell components, particularly the sulfhydryl groups that are susceptible to oxidation. Oxidized Hb denatures and precipitates, forming Heinz bodies, which can damage the cell membrane sufficiently to cause intravascular hemolysis. Other cells, which are not damaged by the oxidized Hb, nevertheless suffer from a loss of deformability, and their cell membranes are further damaged when they pass through the splenic sinusoids and are destroyed by the phagocytes (extravascular hemolysis). All of these changes predispose the red cells to hemolysis.



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Figure 12-7 Peripheral blood smear from a patient with glucose-6-phosphate dehydrogenase deficiency after exposure to oxidant drugs. The image shows red blood cells with precipitates of denatured globin (Heinz bodies) revealed by supravital staining. As the splenic macrophages pluck these cells from the peripheral blood smear, spherocytes are produced. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center)

Drug-induced hemolysis is acute and of variable clinical severity. Typically, patients develop evidence of hemolysis within 1 to 3 days. Because the G6PD gene is on the X chromosome, all the red cells of affected males are deficient in G6PD activity. In contrast, heterozygous females have two distinct populations of red cells: one normal and the other deficient in G6PD activity. Thus, affected males are more vulnerable to oxidant injury, while heterozygous females are usually asymptomatic, except those with a very large proportion of deficient red cells (a chance situation). In the heterozygous state (G6PD A<sup>+</sup>/A<sup>-</sup>), the enzyme deficiency is most marked in older red cells, which are thus more susceptible to oxidative injury. Because the bone marrow compensates by producing new (young) resistant red cells, hemolysis tends to abate even if drug exposure continues. In the homozygous state (G6PD A<sup>-</sup>/A<sup>-</sup>), the enzyme deficiency and the hemolytic effect of oxidants are more severe.

### **Paroxysmal Nocturnal Hemoglobinuria**

A rare disorder of unknown etiology, paroxysmal nocturnal hemoglobinuria (PNH) is mentioned here because of its association with drug-induced hemolysis.



hemolytic anemia that results from an *acquired membrane defect secondary to a mutation that affects a gene, called PIGA*, is required for the synthesis of a specific type of intramembranous glycolipid at which is a component of diverse membrane-associated proteins. Without the membrane anchor, it is not expressed on the surface of cells. The affected proteins include several that limit the spontaneous hemolysis of cells. As a result, PIG-deficient precursors give rise to red cells that are inordinately sensitive to osmotic lysis. It is believed that the hemolysis is nocturnal because the blood becomes acidic during sleep (because of increased lactic acid production) which promotes hemolysis. It is not known why red cell destruction is paroxysmal. Several other PIG-deficient membranes of granulocytes and platelets, possibly explaining the striking susceptibility of these populations to spontaneous thromboses.

PIGA is X-linked, and thus normal cells have only a single active PIGA gene, mutation of which is lethal. Because all myeloid lineages are affected in PNH, the responsible mutations must occur in a multipotential stem cell. Not all, normal individuals harbor small numbers of PIG-deficient bone marrow cells that have mutated. It is believed that clinically evident PNH occurs only in rare instances in which the PIG-deficient clone expands in the setting of primary bone marrow failure (aplastic anemia), which appears most often to be caused by the suppression of marrow stem cells. It is hypothesized that in PNH patients, autoreactive T cells suppress PIG-deficient antigens on normal bone marrow progenitors. Because PIG-deficient stem cells do not express the antigens, they eventually replace the normal marrow elements. Therapy with an antibody that inhibits the CD33 antigen (thereby red cell hemolysis) is currently under evaluation.

### Immuno-hemolytic Anemias

Antibodies that recognize determinants on red cell membranes cause these uncommon forms of hemolytic anemia. They arise spontaneously or be induced by exogenous agents such as drugs or chemicals. Immunohemolytic anemia is characterized by (1) the nature of the antibody and (2) the presence of certain predisposing conditions (summarized in Table 12-4).

**Table 12-4. Classification of Immuno-hemolytic Anemias**

<b>Warm Antibody Type</b>
Primary (idiopathic)
Secondary: B-cell lymphoid neoplasms (e.g., chronic lymphocytic leukemia), autoimmune disorders (e.g., SLE) (e.g., α-methyl-dopa, penicillin, quinidine)
<b>Cold Antibody Type</b>
Acute: <i>Mycoplasma</i> infection, infectious mononucleosis
Chronic: idiopathic, B-cell lymphoid neoplasms (e.g., lymphoplasmacytic lymphoma)

Whatever the cause of antibody formation, the diagnosis of immuno-hemolytic anemias depends on the demonstration of complement on patient red cells. This is done using the *direct Coombs antiglobulin test*, which measures the ability of antibodies in the patient's serum to agglutinate red cells from the patient. In animals against human immunoglobulins or complement to agglutinate red cells from the patient. Patient serum is tested for the ability to agglutinate defined red cells, can then be used to characterize the antibody.

#### Warm Antibody Immuno-hemolytic Anemias

These are caused by immunoglobulin G (IgG) or, rarely, immunoglobulin A (IgA) antibodies that attack red cells. In some cases are idiopathic (primary), while another 25% are associated with an underlying disease affecting the immune system (e.g., lupus erythematosus [SLE]) or are induced by drugs. *The hemolysis usually results from the opsonization of red cells by autoantibodies*, which leads to erythrophagocytosis in the spleen and elsewhere. Spheroidal cells (spherocytes) are often found in the peripheral blood smear. Presumably, cell membrane is removed from antibody-coated cells. This reduces the surface area-to-volume ratio and leads to the formation of spherocytes in the spleen, as described earlier. The clinical severity of immuno-hemolytic anemias is quite variable, ranging from mild anemia with moderate splenomegaly and often require no treatment.

The mechanisms of hemolysis induced by drugs are varied and in some cases poorly understood. In some cases, autoantibodies that are directed against intrinsic red cell antigens, in particular Rh blood group antigens, are indistinguishable from primary idiopathic immuno-hemolytic anemia. Presumably, the drug alters the antigenic properties of the red cell membrane.

of T-cell tolerance to the membrane proteins (see [Chapter 5](#)). In other cases, drugs such as penicillin elicit an antibody response by binding to a red cell membrane protein. Sometimes antibodies bind to drug-antigen complexes, which are then deposited on red cell membranes. Here they may fix complement or otherwise damage red cells and lead to hemolysis.

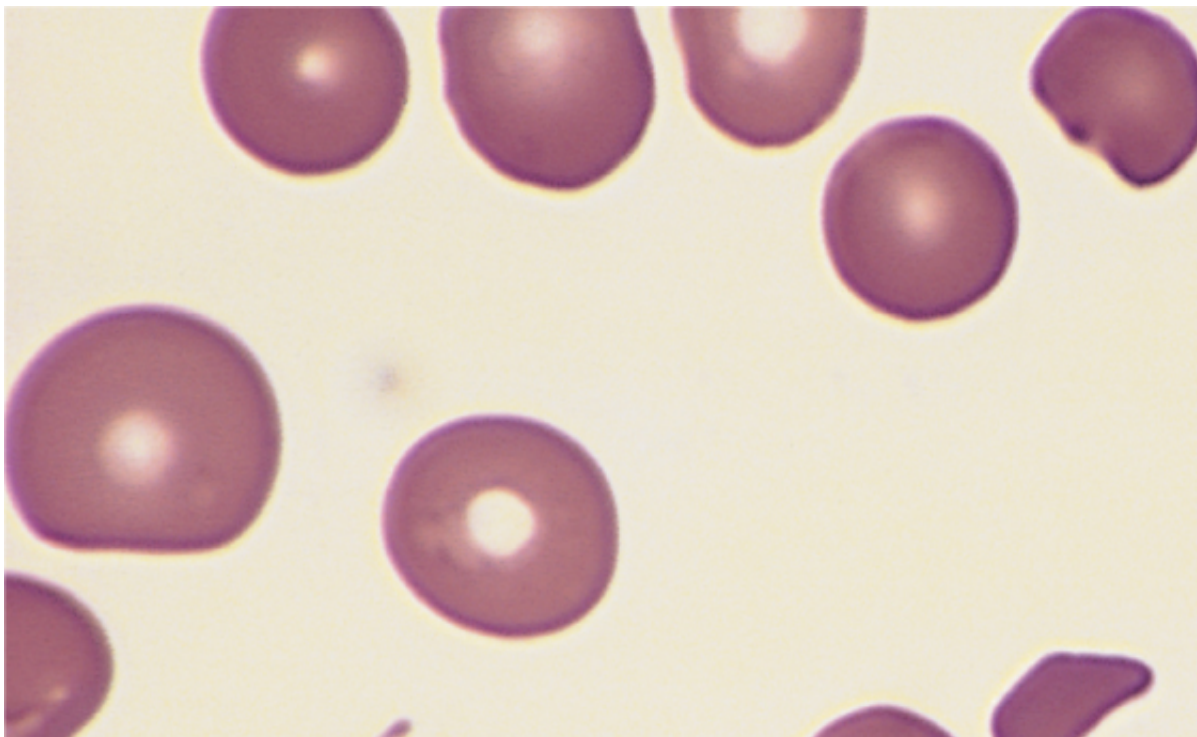
#### *Cold Antibody Immuno-hemolytic Anemias*

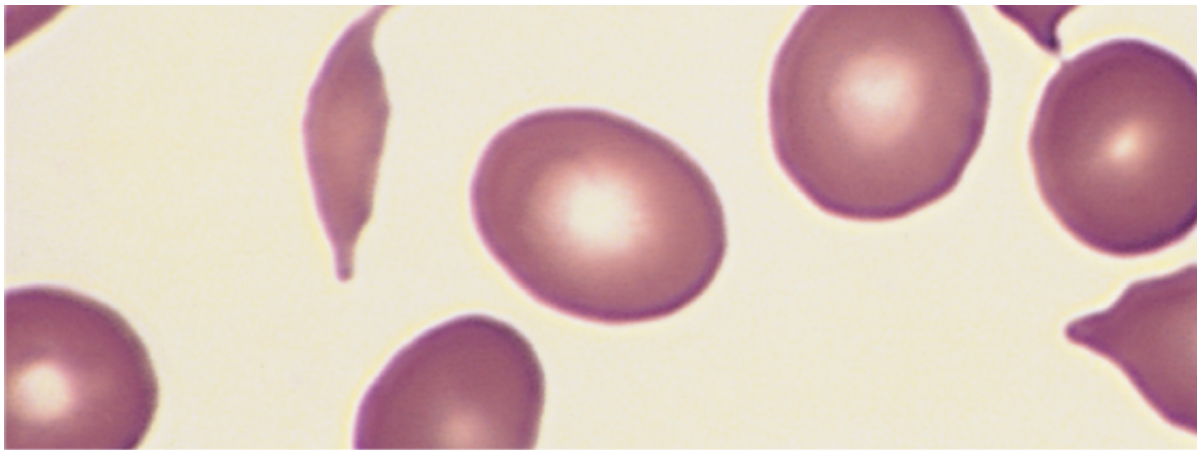
These anemias are caused by low-affinity immunoglobulin M (IgM) antibodies, which bind to red cells at temperatures below 30°C, which are commonly experienced in distal parts of the body (e.g., ears, hands, and feet). The later steps of complement fixation occur inefficiently at temperatures below 37°C. As a result, red cells are coated with C3b but are not lysed in the periphery. When these cells travel to warmer areas, the weakly bound coating of C3b remains. Because C3b is an opsonin ([Chapter 2](#)), the cells are phagocytosed by macrophages, especially Kupffer cells; hence, the *hemolysis is extravascular*. Cold agglutinins sometimes develop in patients with pneumonia caused by *Mycoplasma* sp. and infectious mononucleosis, producing a mild anemia. Cold agglutinin hemolytic anemia occurs in association with lymphoid neoplasms or as an idiopathic condition. A similar phenomenon often occurs in these patients as a result of the agglutination of red cells in the capillaries.

#### **Hemolytic Anemias Resulting from Mechanical Trauma to Red Cells**

Red cells are disrupted by physical trauma in a variety of circumstances. Clinically important hemolytic anemias can result from cardiac valve prostheses or by the narrowing and partial obstruction of the vasculature. *Traumatic hemolytic anemia* can occur incidentally following any activity that produces repeated physical blows (e.g., marathon racing and boxing). It is of importance mainly in patients with mechanical heart valves, which can cause sufficiently turbulent flow to damage red cells. *Microangiopathic hemolytic anemia* is observed in a variety of pathologic states in which small vessels are damaged. The most frequent of these conditions is disseminated intravascular coagulation (DIC; see later), in which there is widespread intravascular deposition of fibrin. Other causes of microangiopathic hemolytic anemia include malignant hypertension, thrombocytopenic purpura, hemolytic-uremic syndrome, and disseminated cancer, all of which produce mechanical injury to the circulating red cells. The morphologic alterations in the injured red cells (schistocytes) are characteristic; "burr cells," "helmet cells," and "triangle cells" may be seen ([Fig. 12-8](#)). While the presence of schistocytes often provides an important diagnostic clue, in and of itself it is not usually a major clinical problem.

#### **Malaria**





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Figure 12-8 Microangiopathic hemolytic anemia. The peripheral blood smear from a patient with hemolytic-uremic (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern

It has been estimated that 200 million persons suffer from this infectious disease, which is one of humans. Malaria is endemic in Asia and Africa, but with widespread jet travel, cases now occur all over the world. There are four types of protozoa. Of these, the most important is *Plasmodium falciparum*, which causes the most serious disorder with a high fatality rate. The other three species of *Plasmodium* that infect humans cause relatively benign disease. All forms are transmitted only by the bite of female *Anopheles* mosquitoes, which are the natural reservoir.

#### *Etiology and Pathogenesis*

The life cycle of plasmodia is complex. As mosquitoes feed on human blood, sporozoites are introduced into the body. Within minutes they infect liver cells. Here, the parasites multiply rapidly to form a schizont containing thousands of parasites. After several weeks that varies with the *Plasmodium* species, the infected hepatocytes release the parasites. Intraerythrocytic parasites either continue asexual reproduction to produce more merozoites or give rise to gametocytes, which infect the next hungry mosquito. During their asexual reproduction in red cells, the parasites form a ring, which is somewhat distinctive for each of the four forms of malaria. Thus, *the species of malaria that is responsible for the disease is appropriately stained thick smears of peripheral blood*. The asexual phase is completed when the merozoites, which escape by lysing the red cells.

#### *Clinical Features*

The distinctive clinical and anatomic features of malaria are related to the following:

Shows of new merozoites are released from the red cells at intervals of approximately 48 hours for *P. falciparum*, and 72 hours for *P. malariae*. The clinical spikes of shaking, chills, and fever occur because large numbers of red cells are destroyed and thus cause hemolytic anemia. A characteristic brownish color of Hb that is identical to hematin, is released from the ruptured red cells along with the merozoites. The liver, lymph nodes, and bone marrow. Activation of the phagocytic defense mechanism leads to hyperplasia of the mononuclear phagocyte system throughout the body, reflected in massive enlargement of the liver may also be enlarged.

*Fatal falciparum malaria often involves the brain, a complication known as cerebral malaria.* Normal red blood cells interact poorly with endothelial cells. Infection of red cells with *P. falciparum* induces the formation of surface knobs containing parasite-encoded proteins, which bind to adhesion molecules expressed on the endothelial cell. Endothelial cell adhesion molecules have been proposed to mediate this interaction, including integrins. This leads to the sequestration of red cells in postcapillary venules. In the brain this process gives rise to the formation of parasitized red cells and often occluded by microthrombi. Cerebral malaria is rapidly progressive and often occurs within days to weeks. Fortunately, *falciparum malaria* more commonly pursues a more chronic course. A dramatic complication known as *blackwater fever*. The trigger for this uncommon complication

massive hemolysis, leading to jaundice, hemoglobinemia, and hemoglobinuria.

With appropriate chemotherapy, the prognosis for patients with most forms of malaria is good; however, it is becoming more difficult, as a result of the emergence of drug-resistant strains. Because of the potential for a fatal disease, early diagnosis and treatment are particularly important but are sometimes delayed in developing countries. There is no effective vaccine, which is long sought but still elusive.

## SUMMARY

### Hemolytic Anemias

#### *Hereditary Spherocytosis:*

Autosomal dominant disorder caused by inherited mutations that affect the red cell cytoskeleton, leading to loss of membrane and eventual conversion of red cells into spherocytes, which are phagocytosed and removed in the spleen. Manifested by a chronic hemolytic anemia.

#### *Sickle Cell Anemia:*

Autosomal recessive disorder that results from a mutation in  $\beta$ -globin that causes deoxygenated hemoglobin to self-associate into long polymers that distort the red cell. Blockage of vessels by aggregates of sickled cells causes acute infarction. Red cell membrane damage that attends repeated bouts of infarction leads to moderate to severe hemolytic anemia.

#### *Thalassemias:*

Group of autosomal co-dominant disorders in which mutations in the genes for hemoglobin synthesis, causing a microcytic, hypochromic anemia. Unpaired  $\alpha$ -globin chains form aggregates that damage red cell precursors and suppress erythropoiesis.

#### *Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency:*

X-linked disorder in which red cells are unusually susceptible to damage by oxidative stress.

#### *Immuno-hemolytic Anemias:*

Caused by antibody binding to red cell surface antigens, which may be intrinsic constituents or antigens that are modified by haptens (such as drugs). Result in red cell opsonization and phagocytosis in the spleen or complement-mediated intravascular hemolysis.







## ANEMIAS OF DIMINISHED ERYTHROPOIESIS

This category includes anemias that are caused by an inadequate dietary supply of substances that are particularly iron, [folic acid](#), and vitamin B<sub>12</sub>. Other disorders that suppress erythropoiesis include failure (aplastic anemia) or the replacement of the bone marrow by tumor or inflammatory cells (myelofibrosis). In this section, some common examples of anemias resulting from nutritional deficiencies and marrow failure are discussed.

### Iron Deficiency Anemia

It is estimated that anemia affects about 10% of the population in developed countries and 25% to 30% in developing countries. In all settings, the most common cause of anemia is iron deficiency, which is without question *the most common*. The factors responsible for iron deficiency differ in various populations and can be best considered in the context of iron metabolism.

Total body iron content is about 2 gm for women and 6 gm for men. Approximately 80% of this is in the form of hemoglobin, the remainder being found in myoglobin and iron-containing enzymes (e.g., catalase and cytochrome c). About 10% of the body iron is stored as hemosiderin and ferritin-bound iron, contains on average 15% to 20% of total body iron. Stores are found in the liver, bone marrow, and skeletal muscle. Because *serum ferritin* is largely derived from the storage pool in the liver, it is a useful indicator of the adequacy of body iron stores. *Assessment of bone marrow iron stores* is another method for estimating body iron content. Iron is transported in the plasma by an iron-binding protein called *transferrin*, which is about 33% saturated with iron, yielding serum iron levels that average 120 µg/dL in men and 100 µg/dL in women. The binding capacity of serum is in the range of 300 µg/dL to 350 µg/dL.

As might be expected given the very high prevalence of iron deficiency in human populations, even the most efficient metabolic pathways that are strongly biased toward the retention of iron. There is no regulated pathway for the loss of iron; the 1 to 2 mg/day that is lost by the shedding of mucosal and skin epithelial cells is replaced by *iron balance*, which is regulated by the absorption of dietary iron. The normal daily western diet contains 10 mg to 20 mg of iron, with about 50% contained in animal products, with the remainder being inorganic iron in vegetables. About 20% of the iron in the diet (nonheme iron) is absorbable, so the average western diet contains sufficient iron to balance fixed losses.

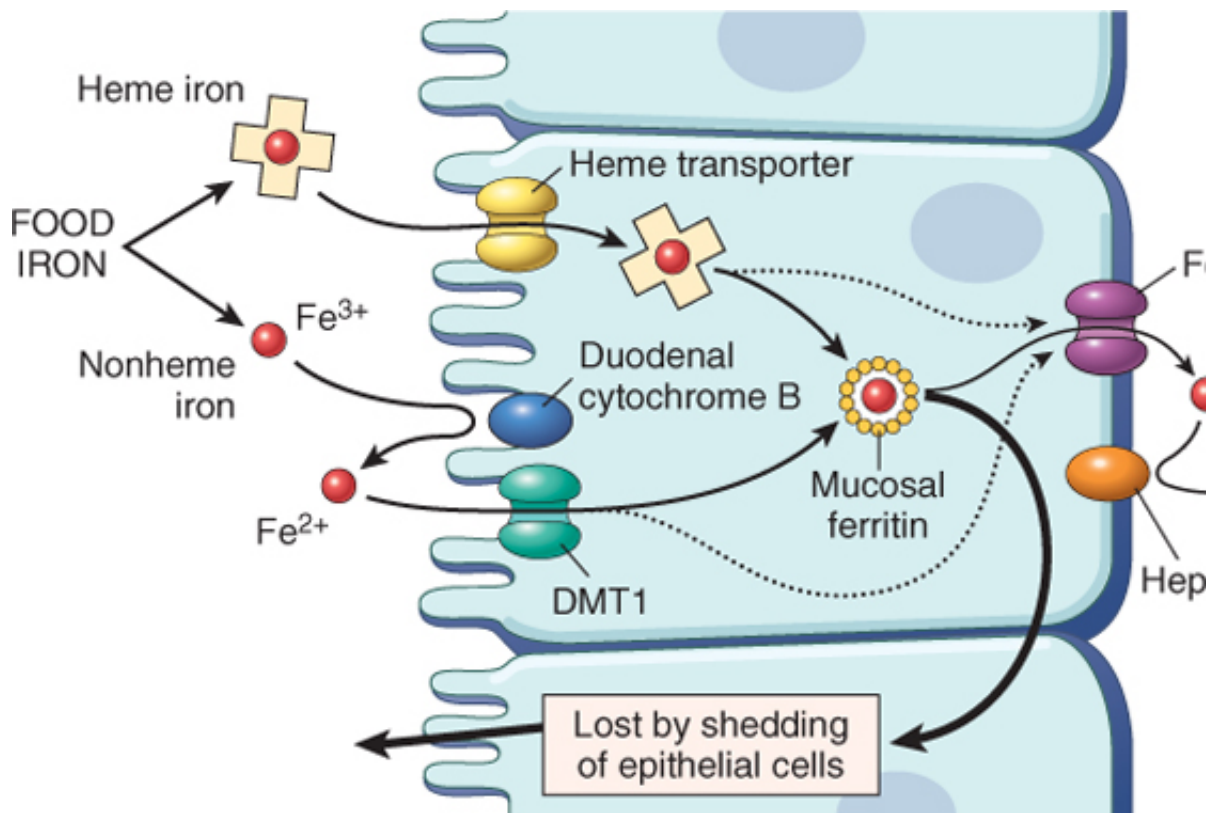
Iron is absorbed in the duodenum, where it must pass through the apical and basolateral membranes of the enterocyte. Iron is carried across each of these two membranes by distinct transporters. After reduction by ferrireductase, iron is transported by the divalent metal transporter (DMT1) across the apical membrane into the cytoplasm. In the cytoplasm, iron is then required for the basolateral transfer of iron to transferrin in the plasma: ferroportin, which acts as a transporter. Both DMT1 and ferroportin are widely distributed in the body and are involved in iron homeostasis. As depicted in [Figure 12-9](#), only a fraction of the iron that enters the cell is delivered to plasma transferrin; the remainder is bound to ferritin and lost through the exfoliation of mucosal cells.

When the body is replete with iron, most of the iron that enters duodenal cells is bound to ferritin and is not available for transfer to plasma transferrin. In iron deficiency, or when there is ineffective erythropoiesis, transfer to plasma transferrin is enhanced. This is regulated by a small hepatic peptide that is synthesized and secreted in an iron-dependent fashion. Plasma hepcidin levels regulate the internalization and degradation of ferroportin; thus, when hepcidin concentrations are high, ferroportin levels fall and the transfer of iron from enterocytes to transferrin is reduced. Conversely, when hepcidin levels are low, as occurs in hemochromatosis, the transfer of iron from enterocytes to plasma is increased, resulting eventually in systemic iron overload.

Negative iron balance and consequent anemia can result from a variety of causes:

Low dietary intake alone is rarely the cause of iron deficiency in the United States, because the average intake of 10 mg to 20 mg is more than enough for males and adequate for females. In other parts of the world, however, low bioavailability from predominantly vegetarian diets are an important cause of iron deficiency. Iron deficiency can also result from celiac disease or after gastrectomy ([Chapter 15](#)). Increased demands not met by normal diet, as in pregnancy and infancy. Chronic blood loss is the most important cause of iron deficiency anemia.

occur from the gastrointestinal tract (e.g., peptic ulcers, colonic cancer, hemorrhoids, hook (e.g., menorrhagia, metrorrhagia, cancers).



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Figure 12-9 Iron absorption. Mucosal uptake of heme and nonheme iron is depicted. When the storage sites of the body are normal, most of the absorbed iron is lost into the gut by shedding of the epithelial cells. Conversely, when erythropoiesis is stimulated, a greater fraction of the absorbed iron is transferred into plasma transferrin, with a corresponding decrease in mucosal ferritin. DMT1, divalent metal transporter 1.

Regardless of the cause, iron deficiency develops insidiously. At first iron stores are depleted, leading to the absence of stainable iron in the bone marrow. This is followed by a decrease in serum iron and a decrease in transferrin saturation. Ultimately the capacity to synthesize hemoglobin, myoglobin, and other iron-containing proteins is reduced, leading to decreased work and cognitive performance, and even reduced immunocompetence.

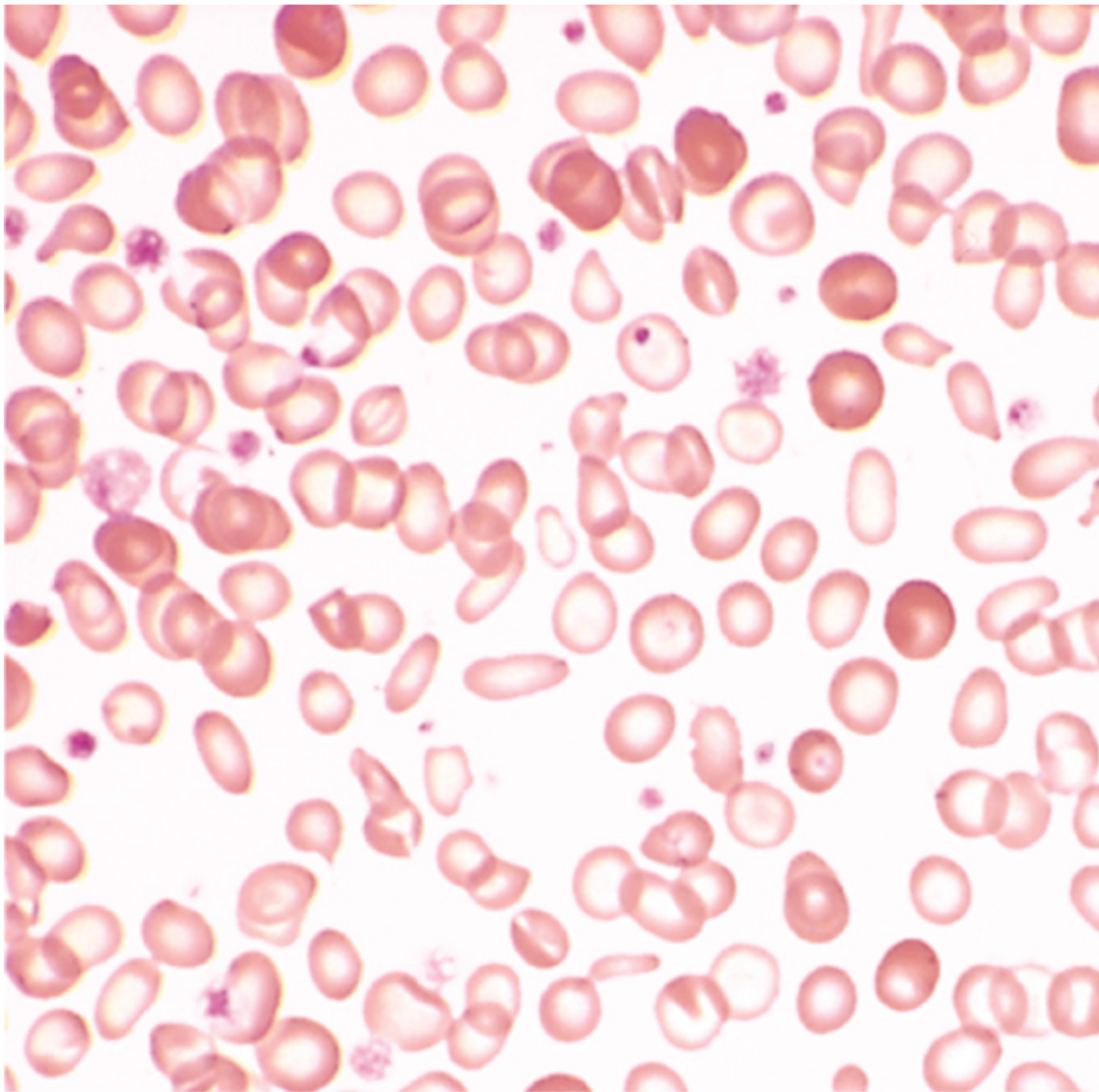
### Morphology

Except in unusual circumstances, iron deficiency anemia is relatively mild. The red blood cells are **hypochromic**, reflecting the reductions in MCV and MCHC (Fig. 12-10). For unclear reasons, the platelet count is often accompanied by an increase in the platelet count. Although erythropoietin levels are increased, the marrow response is blunted by the iron deficiency, and thus the marrow cellularity is decreased. Extramedullary hematopoiesis is uncommon.

### Clinical Course

In most instances, iron deficiency anemia is asymptomatic. Nonspecific manifestations, such as fatigue and weakness, are present in severe cases. With long-standing severe anemia, thinning, flattening, and eventually "beak" deformities of the nails appear. A curious but characteristic neurobehavioral complication is *pica*, the compulsion to consume nonfood substances.





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Figure 12-10 Hypochromic microcytic anemia of iron deficiency. Note the small red cells containing a narrow rim of hemoglobin. Also scattered, fully hemoglobinized cells derived from a recent blood transfusion given to the patient. (Courtesy of Dr. [Name], University of Texas Southwestern Medical School, Dallas, Texas.)

**Diagnostic criteria** include anemia, hypochromic and microcytic red cell indices, low serum ferritin, low transferrin saturation, increased total iron-binding capacity, and, ultimately, response to iron therapy. Person but rarely of it. It is important to remember that in reasonably well-nourished persons, microcytic h rather a symptom of some underlying disorder.

### Anemia of Chronic Disease

This is the most common form of anemia in hospitalized patients. It superficially resembles the an inflammation-induced sequestration of iron within the cells of the mononuclear phagocyte (reticuloendothelial system) of chronic inflammatory disorders, including the following:

Chronic microbial infections, such as osteomyelitis, bacterial endocarditis, and lung abscesses; rheumatoid arthritis and regional enteritis; Neoplasms, such as Hodgkin lymphoma and carcinoma.

inflammatory and regional enterocolitides, such as Hodgkin lymphoma and sarc

The serum iron levels are usually low, and the red cells can be normocytic and normochromic, or, hypochromic and microcytic. However, the anemia of chronic disease is associated with *increased serum ferritin concentration, and a reduced total iron-binding capacity*, all of which readily rule out findings attributable to high concentrations of circulating hepcidin, which inhibits ferroportin and mononuclear phagocyte storage pool to the erythroid precursors. The elevated hepcidin concentration is due to cytokines, which enhance the synthesis of hepcidin by the liver. In addition, chronic inflammation suppresses erythropoietin levels, which is not adequate for the degree of anemia. The teleologic explanation for the wide variety of chronic inflammatory disorders is unclear; it may serve to inhibit the growth of iron-augment certain aspects of host immunity. Administration of erythropoietin and iron can improve the condition; the underlying condition is curative.

### Megaloblastic Anemias

There are two principal causes of megaloblastic anemia: folate deficiency and vitamin B<sub>12</sub> deficiency. The effects of their deficiency on hematopoiesis are quite similar. However, the consequences of folate and vitamin B<sub>12</sub> deficiency differ in important ways.

#### Pathogenesis

The morphologic hallmark of megaloblastic anemias is an enlargement of erythroid precursors (*m* abnormally large red cells (macrocytes). The other myeloid lineages are also affected. Most notably, *giant metamyelocytes* and yield highly characteristic *hypersegmented neutrophils*. Underlying the defect is impaired DNA synthesis, which results in a delay in nuclear maturation and cell division. Because the synthesis of cytoplasmic components proceeds at a normal rate and thus outpaces that of the nucleus, the hematopoietic precursors show maturational derangement contributes to anemia in several ways. Some megaloblasts are so defective that they undergo apoptosis in the marrow (ineffective hematopoiesis). Others succeed in maturing into red cells but result, the total output from these precursors is diminished. Granulocyte and platelet precursors are also affected. Patients with megaloblastic anemia develop pancytopenia (anemia, thrombocytopenia, and granulocytopenia).

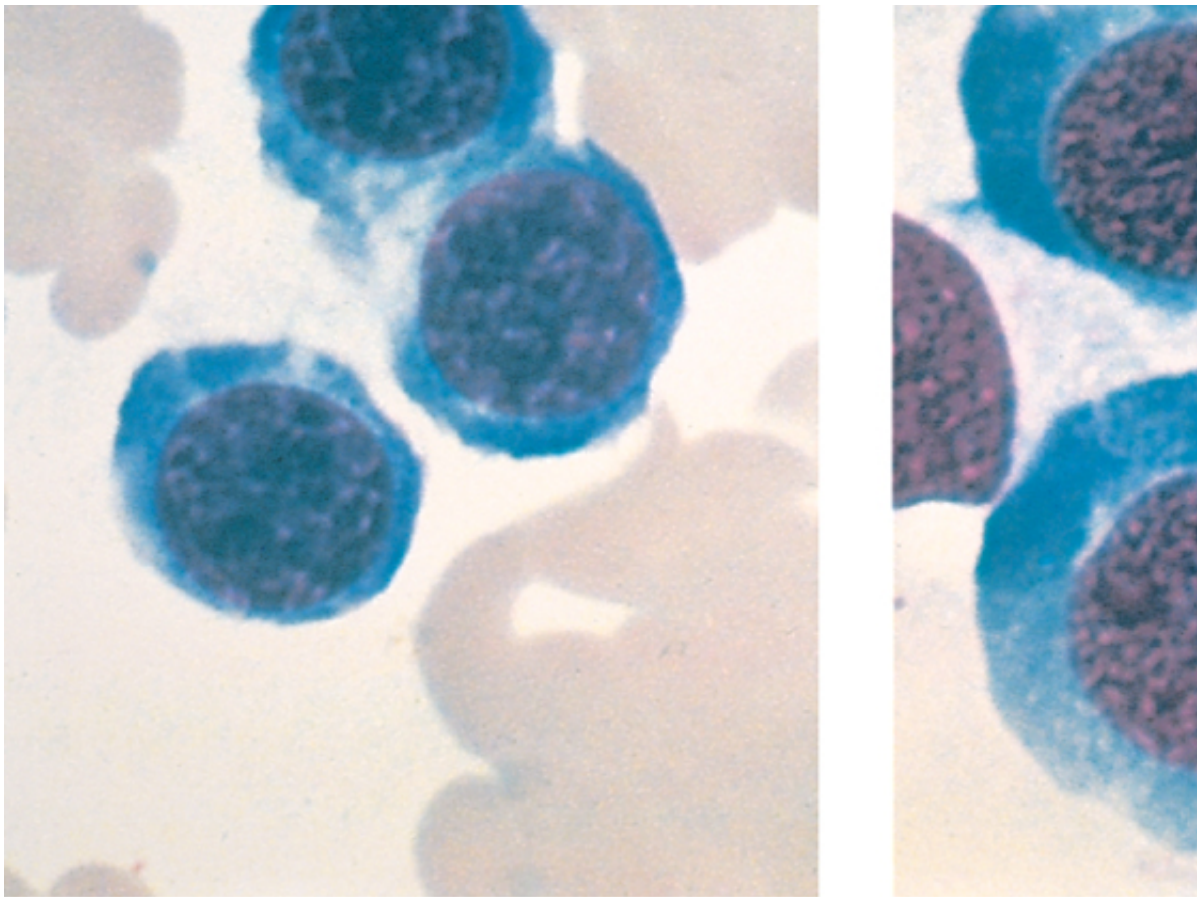
#### Morphology

Certain morphologic features are common to all forms of megaloblastic anemias. The marrow is markedly hypercellular, as a result of increased numbers of **megaloblasts**. These precursors have a delicate, finely reticulated nuclear chromatin (suggestive of a normoblast) and have a delicate, finely reticulated nuclear chromatin (suggestive of a normoblast) and have a delicate, finely reticulated nuclear chromatin (suggestive of a normoblast) and have a delicate, finely reticulated nuclear chromatin (suggestive of a normoblast). As the megaloblasts differentiate and acquire hemoglobin, the nucleus retains its finely distributed chromatin and fails to clump, a feature typical of an orthochromatic normoblast. Similarly, the granulocytic precursors show nuclear-cytoplasmic asynchrony, yielding giant metamyelocytes. Megakaryocytes are also present, large and have bizarre multilobed nuclei.

In the **peripheral blood** the earliest change is usually the appearance of **hypersegmented neutrophils**, which appear even before the onset of anemia. Normally, neutrophils have three or four segments; in megaloblastic anemias neutrophils often have five or more. **The red cells typically are macrocytic; the MCV is often greater than 110 fL** (normal, 82-92 fL). They may appear hyperchromic, in reality the MCHC is normal. Large, misshapen platelets may be present. Morphologic changes in other systems, especially the gastrointestinal tract, also occur. The clinical features are discussed in the next section.







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Figure 12-11 Comparison of normoblasts (*left*) and megaloblasts (*right*). The megaloblasts are larger, have relaxed chromatin, and have an abundant basophilic cytoplasm. (Courtesy of Dr. José Hernandez, Department of Pathology School, Dallas, Texas.)

### **Folate (Folic Acid<sup>®</sup>) Deficiency Anemia**

Megaloblastic anemia secondary to folate deficiency is not common, but marginal folate stores occur in apparently healthy individuals. The risk of clinically significant folate deficiency is high in those with the indigent, and the elderly) or increased metabolic needs (pregnant women and patients with chronic

Ironically, folate is widely prevalent in nearly all foods but is readily destroyed by 10 to 15 minutes of cooking. Folate are fresh uncooked vegetables and fruits. Food folates are predominantly in polyglutamate form; for absorption, a conversion to monoglutamates is required, a conversion that is hampered by acidic foods and substances like **Phenytoin<sup>®</sup>** (Dilantin) and a few other drugs also inhibit folate absorption, while others, such as methotrexate. The principal site of intestinal absorption is the upper third of the small intestine; thus, malabsorption of the gut, such as celiac disease and tropical sprue, can impair folate uptake.

The metabolism and physiologic functions of folate are complex. Here, it is sufficient to note that, in the blood mainly as a monoglutamate. Within cells it is further metabolized to several derivatives, tetrahydrofolate by the enzyme dihydrofolate reductase is particularly important. Tetrahydrofolate provides carbon units in a variety of steps involved in the synthesis of purines and thymidylate, the building blocks of DNA. This accounts for the inadequate DNA synthesis that is characteristic of megaloblastic anemia.

The onset of the anemia is insidious and is associated with nonspecific symptoms such as weakness. The picture may be complicated by the coexistent deficiency of other vitamins, especially in alcoholics. The hematopoietic system, being a site of rapid cell turnover, symptoms referable to the alimentary tract

include sore tongue and cheilosis. *It should be stressed that, unlike in vitamin B<sub>12</sub> deficiency, neu*

The diagnosis of a megaloblastic anemia is readily made from examination of a smear of peripheral blood. The diagnosis of folate deficiency is best distinguished from that of vitamin B<sub>12</sub> deficiency by measuring serum

### ***Vitamin B<sub>12</sub> (Cobalamin) Deficiency Anemia: Pernicious Anemia***

Inadequate levels of vitamin B<sub>12</sub>, or cobalamin, result in a megaloblastic macrocytic anemia similar to that of folate deficiency. However, vitamin B<sub>12</sub> deficiency can also cause a demyelinating disorder involving the peripheral nervous system and, importantly, the spinal cord. There are many causes of vitamin B<sub>12</sub> deficiency. The term *pernicious anemia*, a cause and therapy of this condition were unknown, is used to describe vitamin B<sub>12</sub> deficiency resulting from a defective function of intrinsic factor. Intrinsic factor plays a critical role in the absorption of vitamin B<sub>12</sub>. The process proceeds as follows:

1. Peptic digestion releases dietary vitamin B<sub>12</sub>, which then binds to salivary B<sub>12</sub>-binding protein.
2. R-B<sub>12</sub> complexes are transported to the duodenum and processed by pancreatic protease; the vitamin is released and intrinsic factor secreted from the parietal cells of the gastric fundic mucosa.
3. The intrinsic factor-B<sub>12</sub> complex passes to the distal ileum and attaches to the epithelial intestinal receptor, initiating absorption of vitamin B<sub>12</sub>.
4. The absorbed B<sub>12</sub> is bound to transport proteins called *transcobalamins*, which then deliver it to the tissues.

### ***Etiology***

*Among the many potential causes of cobalamin deficiency, long-standing malabsorption is the most common. Vitamin B<sub>12</sub> is abundant in all animal foods, including eggs and dairy products, and is resistant to cooking and to acid. Plant foods, water and nonanimal foods can provide adequate amounts. As a result, deficiencies due to diet are rare. Vegans. Once vitamin B<sub>12</sub> is absorbed, the body handles it very efficiently. It is stored in the liver, in amounts sufficient to support bodily needs for 5 to 20 years.*

Until proved otherwise, *a deficiency of vitamin B<sub>12</sub> (in the western world) is caused by pernicious anemia*, an autoimmune reaction against parietal cells and intrinsic factor itself, which produces gastric mucosal atrophy. The associations favor an autoimmune basis:

Autoantibodies are present in the serum and gastric juice of most patients with pernicious anemia. Three types have been found: *parietal canalicular antibodies*, which bind to the mucosal parietal cells; *blocking antibodies*, which block vitamin B<sub>12</sub> to intrinsic factor; and *binding antibodies* that react with intrinsic factor-B<sub>12</sub> complex, preventing it from binding to the ileal receptor. An occurrence of pernicious anemia with other autoimmune diseases such as rheumatoid arthritis and type I diabetes mellitus is well documented. The frequency of serum antibodies to intrinsic factor is higher in other autoimmune diseases.

Chronic vitamin B<sub>12</sub> malabsorption is also seen following gastrectomy (which leads to loss of cells in the gastric mucosa and ileum (which prevents absorption of intrinsic factor-B<sub>12</sub> complex), and in disorders that involve the small intestine (tropical sprue, and Whipple disease). In individuals older than 70 years of age, gastric atrophy and loss of parietal cells, with decreased production of acid and pepsin, which are needed to release the vitamin from its bound form in the food, are common.

The metabolic defects that are responsible for the anemia are intertwined with folate metabolism. Folate deficiency leads to megaloblastic anemia, and hence its deficiency reduces the availability of the form of folate that is required for DNA synthesis. Given this relationship, the anemia of vitamin B<sub>12</sub> deficiency improves with administration of folate. However, the neuropathy in vitamin B<sub>12</sub> deficiency is unclear, and administration of folate may actually exacerbate it. The principal neurologic lesions associated with vitamin B<sub>12</sub> deficiency are *demyelination of the posterior columns and lateral funiculi*, sometimes beginning in the peripheral nerves. In time, axonal degeneration may supervene. The severity of the neuropathy is not related to the degree of anemia. Indeed, uncommonly, the neurologic disease occurs in the absence of anemia.

not related to the degree of anemia. Indeed, anorexia, and neurologic disease occur in the an

### **Clinical Features**

Manifestations of vitamin B<sub>12</sub> deficiency are nonspecific. As with any other anemia, there is pallor, dyspnea and even congestive heart failure. The increased destruction of erythroid progenitors may cause. Gastrointestinal symptoms similar to those seen in folate deficiency are seen. The spinal cord dysfunction, tingling, and burning in feet or hands, followed by unsteadiness of gait and loss of position sense, anemia responds dramatically to parenteral vitamin B<sub>12</sub>, the neurologic manifestations often fail to respond. Patients with pernicious anemia have an increased risk of gastric carcinoma.

The diagnostic features of pernicious anemia include (1) low serum vitamin B<sub>12</sub> levels, (2) normal serum antibodies to intrinsic factor, (4) moderate to severe megaloblastic anemia, (5) leukopenia, (6) a dramatic reticulocytic response (within 2-3 days) to parenteral administration of vitamin B<sub>12</sub>.

### **Aplastic Anemia**

Aplastic anemia is a disorder in which *multipotent myeloid stem cells are suppressed, leading to a*. Notwithstanding its name, aplastic anemia should not be confused with selective suppression of one or more lineages in which anemia is the only manifestation.

#### ***Etiology and Pathogenesis***

In more than half of cases, aplastic anemia is idiopathic. In the remainder, an exposure to known chemicals, can be identified. With some agents, the marrow damage is predictable, dose related, and the categories are antineoplastic drugs (e.g., alkylating agents, antimetabolites), benzene, and chloramphenicol. Toxicity occurs as an apparent "idiosyncratic" or hypersensitivity reaction to small doses of known drugs or to drugs such as sulfonamides, which are not myelotoxic in other persons.

Aplastic anemia sometimes arises after certain viral infections, most often community-acquired viral infections. The responsible virus is not known; hepatitis viruses A, B, and C are apparently not the culprits. Marrow aplasia follows recovery from the hepatitis and follows a relentless course.

The pathogenetic events leading to marrow failure remain vague, but it seems that autoreactive T cells, supported by a variety of experimental data and clinical experience, which has shown that in 70% of cases responds to immunosuppressive therapy aimed at T cells. Much less clear are the events that trigger the disease; perhaps viral antigens, drug-derived haptens, and/or genetic damage create neoantigens within the immune system.

Rare but interesting genetic conditions are also associated with marrow failure. Of note, a small fraction of patients with aplastic anemia have inherited defects in telomerase, which you will recall is needed for the maintenance of telomeres. In these settings intrinsic defects lead directly to damage and senescence of hematopoietic stem cells.

### **Morphology**

The bone marrow in aplastic anemia typically is markedly hypocellular, with greater intertrabecular space being occupied by fat. The limited cellularity often consists of a few plasma cells. These changes are better appreciated in bone marrow biopsy specimen aspirates, which often yield a "dry tap." A number of secondary changes often accompany the anemia. Anemia may cause fatty change in the liver, and thrombocytopenia and granulocytopenia may lead to hemorrhages and bacterial infections, respectively. The requirement for transfusion may lead to hemosiderosis.

### **Clinical Course**

Aplastic anemia affects persons of all ages and both sexes. The slowly progressive *anemia* causes weakness, pallor, and dyspnea. *Thrombocytopenia* often presents with petechiae and ecchymoses. The disease is usually fatal only by frequent and persistent minor infections or by the sudden onset of chills, fever, and prostration. *Anemia from anemia caused by marrow infiltration (myelophthisic anemia)*, *leukemia*, *leukemia*

anemia from anemias caused by marrow infiltration (myelophthitic anemia), aleukemic leukemia, pancytopenia is common to these conditions, their clinical manifestations may be indistinguishable from aplastic anemia. Examination of the bone marrow. *Splenomegaly* is characteristically absent in aplastic anemia; if it is present, the diagnosis of aplastic anemia should be seriously questioned. Typically, the red cells are normocytic and normochromic; reticulocytes are occasionally present; *reticulocytes are reduced in number*.

The prognosis of marrow aplasia is quite unpredictable. As mentioned earlier, withdrawal of toxic causes may lead to recovery. The idiopathic form has a poor prognosis if left untreated. Bone marrow transplantation is a potential cure, especially if performed in nontransfused patients younger than 40 years of age. It is proposed that HLA-matched donors, producing a high engraftment failure rate following bone marrow transplantation. As transplant candidates may benefit from immunosuppressive therapy.

### **Myelophthitic Anemia**

This form of anemia is caused by the extensive replacement of the marrow by tumors or other lesions. Metastatic breast, lung, or prostate cancer, but other cancers, advanced tuberculosis, lipid storage diseases, and some drugs produce a similar clinical picture. The principal manifestations of marrow infiltration include anemia, leukopenia, and thrombocytopenia. The white cell series is less affected. Characteristically, misshapen red cells, some resembling teardrop cells, are present. Immature granulocytic and erythrocytic precursors may also be seen (leukoerythroblastosis), along with increased reticulocytes. Treatment is focused on the management of the underlying condition.

### **SUMMARY**

#### **Anemias of Diminished Erythropoiesis**

##### *Iron Deficiency Anemia:*

Inadequate intake of iron results in insufficient hemoglobin synthesis and the presence of microcytic red cells.

##### *Anemia of Chronic Disease:*

Caused by production of inflammatory cytokines, which cause iron to be sequestered in macrophages, resulting in an anemia that is usually normochromic and normocytic.

##### *Megaloblastic Anemia:*

Caused by deficiencies of folate or vitamin B<sub>12</sub>, which lead to inadequate synthesis of thymidine and defective DNA replication. Results in enlarged abnormal precursors (megaloblasts) in the bone marrow, ineffective hematopoiesis, and pancytopenia.

##### *Aplastic Anemia:*

Caused by bone marrow failure (hypocellularity) due to diverse causes including drugs, toxins and radiation, idiosyncratic reactions to drugs and viruses, and inherited bone marrow failure syndromes.

##### *Myelophthitic Anemia:*

Caused by replacement of the bone marrow by infiltrative processes such as leukemia, carcinoma and granulomatous disease. Leads to the release of early precursors (leukoerythroblastosis) and the appearance of tear-drop red cells in the peripheral blood.

### **Laboratory Diagnosis of Anemias**

The diagnosis of anemia is established by a decrease in the hemoglobin and the hematocrit to levels below normal. In addition, the red cell hemoglobin content and size, anemias can be placed into three major subgroups: normochromic normocytic, hypochromic, and macrocytic. The presence of red cells with a particular morphology, such as spherocytes, provide additional etiologic clues. The specialized tests cited below are particularly important in the diagnosis of certain classes of anemia:

Gel electrophoresis: used to detect abnormal hemoglobins, such as HbS  
Coombs test: used to detect autoimmune hemolytic anemias  
Reticulocyte counts: used to distinguish between anemias caused by red cell destruction (increased production) and bone marrow failure (decreased production)  
Iron indices (serum iron, serum iron-binding capacity, transferrin saturation): used to detect iron deficiency anemia



concentrations): used to distinguish between hypochromic microcytic anemias caused by iron deficiency and thalassemia minor  
Serum and red cell folate and vitamin B<sub>12</sub> concentrations: used to identify causes of megaloblastic anemia  
Plasma unconjugated bilirubin and haptoglobin concentrations: used to support the diagnosis of hemolytic anemia

In isolated anemia, tests performed on the peripheral blood usually suffice to establish a cause. In combination with thrombocytopenia and/or granulocytopenia, it is much more likely to be associated with a systemic disease. In these instances, a marrow examination is often critical for diagnosis.



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## POLYCYTHEMIA

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Polycythemia, or *erythrocytosis*, as it is sometimes referred to, denotes an increase in the blood concentration of red cells, which usually correlates with an increase in the hemoglobin concentration. Polycythemia may be *relative*, when there is hemoconcentration caused by a decrease in plasma volume, or *absolute*, when there is an increase in the total red cell mass. Relative polycythemia results from any cause of dehydration, such as water deprivation, prolonged vomiting, diarrhea, or the excessive use of diuretics. Absolute polycythemia is said to be *primary* when the increase in red cell mass results from an autonomous proliferation of the myeloid stem cells, and *secondary* when the red cell progenitors are proliferating in response to an increase in erythropoietin. Primary polycythemia (polycythemia vera [PCV]) is a clonal, neoplastic proliferation of myeloid progenitors, which is considered later in this chapter with the other myeloproliferative disorders. The increases in erythropoietin that are seen in secondary polycythemias have a variety of causes ([Table 12-5](#)).

**Table 12-5. Pathophysiologic Classification of Polycythemia**

<b>Relative</b>
Reduced plasma volume (hemoconcentration)
<b>Absolute</b>
Primary: Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera); inherited activating mutations in the erythropoietin receptor (rare)
Secondary: Increased erythropoietin levels
Appropriate: lung disease, high-altitude living, cyanotic heart disease
Inappropriate: erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatoma, cerebellar hemangioblastoma); surreptitious erythropoietin use (e.g., in endurance athletes)



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## WHITE CELL DISORDERS

Disorders of white cells include deficiencies (leukopenias) and proliferations, which may be reactive or neoplastic. Reactive proliferation in response to an underlying primary, often microbial, disease is fairly common. Neoplastic disorders, though less common, are more ominous; they cause approximately 9% of all cancer deaths in adults and a staggering 40% in children younger than 15 years. In the following discussion we first describe some non-neoplastic conditions and then consider in some detail the malignant proliferations of white cells.





## NON-NEOPLASTIC DISORDERS OF WHITE CELLS

### Leukopenia

Leukopenia results most commonly from a decrease in granulocytes, which are the most prevalent; they are much less common; they are associated with congenital immunodeficiency diseases or are acquired states, such as advanced human immunodeficiency virus (HIV) infection or treatment with corticosteroids. Leukopenias that affect granulocytes are discussed here.

### Neutropenia/Agranulocytosis

A reduction in the number of granulocytes in blood is known as *neutropenia* or sometimes, when severe, as *agranulocytosis*. Characteristically, the total white cell count is reduced to 1000 cells/ $\mu$ L and in some instances to less than 500 cells/ $\mu$ L. Persons are extremely susceptible to bacterial and fungal infections, which can be severe enough to be fatal.

#### *Etiology and Pathogenesis*

The mechanisms that cause neutropenia can be broadly divided into two categories:

*Inadequate or ineffective granulopoiesis.* Reduced granulopoiesis is a manifestation of general bone marrow failure, as in aplastic anemia and a variety of leukemias. Cancer chemotherapy agents also produce neutropenia by bone marrow aplasia. Alternatively, some neutropenias are isolated, with only the differentiation of granulocytes affected. These forms of neutropenia are most often caused by certain drugs or, more uncommonly, by cytotoxic T cells and natural killer (NK) cells. *Accelerated removal or destruction of neutrophils.* Neutropenia can result from immune-mediated injury to neutrophils (triggered in some cases by drugs), or it may be idiopathic. It can occur in overwhelming bacterial, fungal, or rickettsial infections. An enlarged spleen can accelerate removal of neutrophils.

#### **Morphology**

The anatomic alterations in the bone marrow depend on the underlying basis of the neutropenia. **Hypercellularity** is seen when the neutropenia results from excessive destruction of granulocytes, as occurs in megaloblastic anemia. In contrast, disorders that suppress granulocytopoiesis are associated with **a marked decrease in mature granulocytes in the marrow**. Erythropoiesis and megakaryopoiesis can be normal in these disorders. Neutropenia specifically affects the granulocytes, but with most myelotoxic drugs all marrow elements are affected.

#### *Clinical Course*

The initial symptoms are often malaise, chills, and fever, with subsequent marked weakness and weight loss. They commonly take the form of ulcerating, necrotizing lesions of the gingiva, floor of the mouth, and other sites within the oral cavity (agranulocytic angina). These lesions often show a massive growth of bacteria. In addition to removal of the offending drug and control of infection, administration of granulocyte colony-stimulating factor, which stimulates neutrophil production by the bone marrow, is helpful.

### Reactive Leukocytosis

An increase in the number of white cells is common in a variety of reactive inflammatory states caused by various stimuli. Leukocytoses are relatively nonspecific and can be classified on the basis of the particular cells that are increased. As will be discussed later, in some cases reactive leukocytosis may mimic leukemia. Such leukocytoses are not true malignancies of the white cells. Infectious mononucleosis, a form of lymphocytosis caused by the Epstein-Barr virus, merits separate consideration because it gives rise to a distinctive syndrome.



**Table 12-6. Causes of Leukocytosis**

<b>Neutrophilic Leukocytosis</b>
Acute bacterial infections, especially those caused by pyogenic organisms; sterile inflammation caused by (myocardial infarction, burns)
<b>Eosinophilic Leukocytosis (Eosinophilia)</b>
Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis); certain malignancies (e.g., Hodgkin disease and some non-Hodgkin lymphomas); collagen vascular disease (transient)
<b>Basophilic Leukocytosis (Basophilia)</b>
Rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)
<b>Monocytosis</b>
Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; collagen vascular disease (erythematosis); and inflammatory bowel diseases (e.g., ulcerative colitis)
<b>Lymphocytosis</b>
Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, hepatitis A, cytomegalovirus, Epstein-Barr virus); <i>Bordetella pertussis</i> infection

### **Infectious Mononucleosis**

In the Western world, infectious mononucleosis is an acute, self-limited disease of adolescents and young adults. It is caused by lymphocytotropic EBV, a member of the herpesvirus family. The infection is characterized by (1) fever, (2) lymphadenitis; (2) an increase of lymphocytes in blood, many of which have an atypical morphology. It should be noted that cytomegalovirus infection induces a similar syndrome, with similar clinical and serologic methods.

### **Epidemiology and Immunology**

EBV is ubiquitous in all human populations. Where economic deprivation results in inadequate living conditions, infection is nearly universal. At this age, symptomatic disease is uncommon, and, even though infected hosts shed virus (usually later), more than half continue to shed virus. In contrast, in developed countries that enjoy better living conditions, infection is delayed until adolescence or young adulthood. For reasons that are not clear, only about 20% of children in these countries shed the virus, and only about 50% of those who are exposed to the virus acquire the infection. "Kissing cousin" usually involves direct oral contact. It is hypothesized (but not proven) that the virus is transmitted by infected cells and then spreads to underlying lymphoid tissue (tonsils and adenoids), where B lymphocytes are infected. The infection of B cells takes one of two forms. In a minority of cells, the infection leads to productive infection accompanied by the release of virions. In most cells, however, the infection is nonproductive, and the virus remains as an extrachromosomal episome. *B cells that are latently infected with EBV undergo polyclonal activation* by the action of several EBV proteins (Chapter 6). These cells disseminate in the circulation and secrete antibodies, including the well-known heterophil anti-sheep red cell antibodies that are recognized in diagnostic tests. In early acute infection, EBV is shed in the saliva; it is not known if the source of these virions is oropharyngeal or systemic.

A normal immune response is extremely important in controlling the proliferation of EBV-infected cells. During the course of the infection, IgM, and, later, IgG, antibodies are formed against viral capsid antigens. The control of polyclonal B-cell proliferation are cytotoxic CD8<sup>+</sup> T cells and NK cells. *Virus-specific lymphocytes in the circulation, a finding that is characteristic of acute mononucleosis.* In otherwise healthy individuals, humoral and cellular responses to EBV act as brakes on viral shedding, limiting the number of infected cells. Latent EBV remains in a few B cells and possibly oropharyngeal epithelial cells as well. As will be discussed, failure to have disastrous consequences.

### **Morphology**

The major alterations involve the blood, lymph nodes, spleen, liver, central nervous system, and, occasionally, other organs. There is peripheral blood **leukocytosis**, with a white cell count between 12,000 and 18,000 cells/ $\mu$ L. Typically more than half of these cells are large **lymphocytes**, 12 to 16  $\mu$ m in diameter, with an abundant cytoplasm that often contains vacuoles and an oval, indented, or folded nucleus (Fig. 12-12). These atypical lymphocytes, which are distinctive to suggest the diagnosis, are mainly cytotoxic CD8<sup>+</sup> T cells.

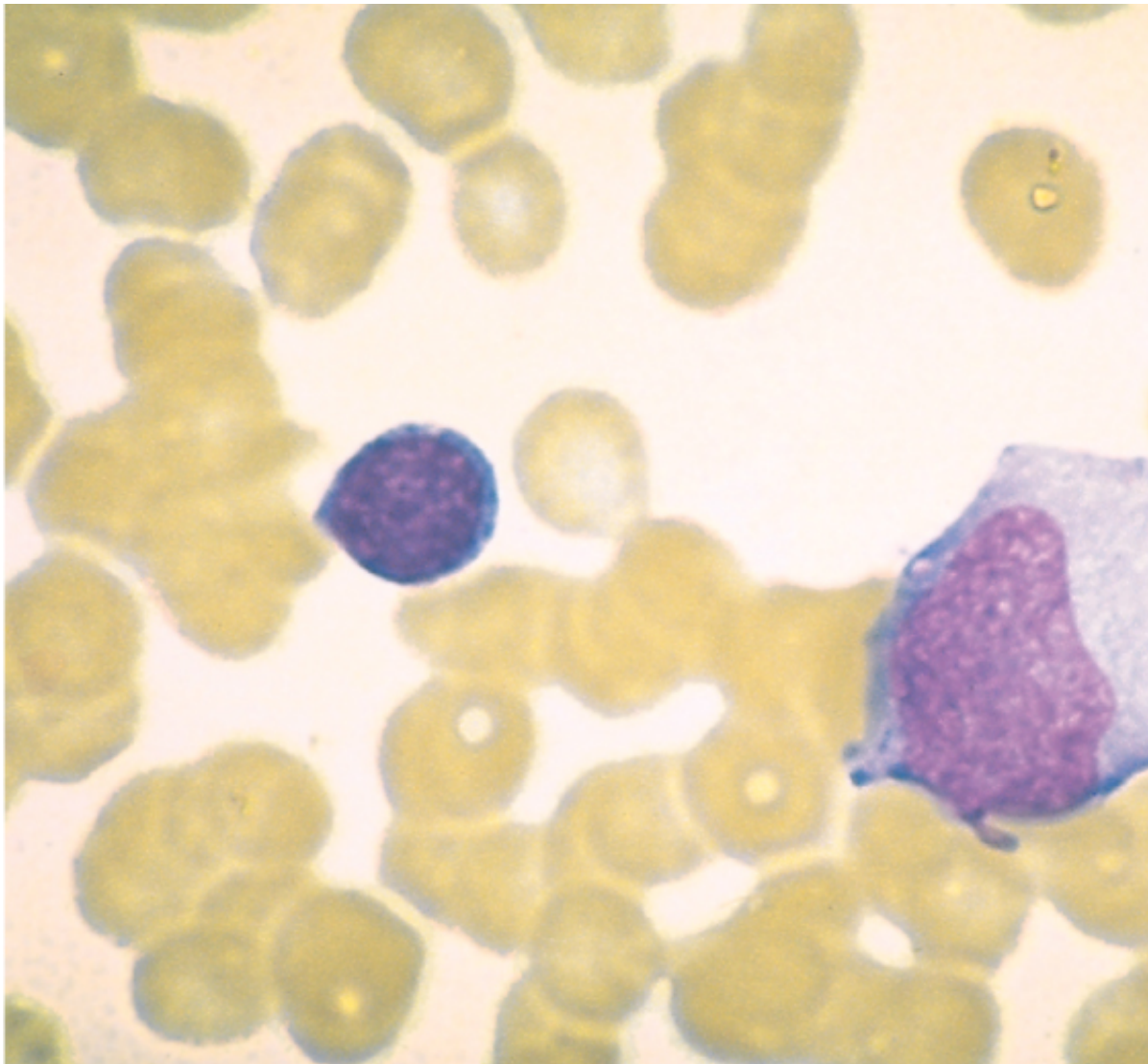
distinctive to suggest the diagnosis, are mainly cytotoxic CD8+ T cells.

The **lymph nodes** are enlarged throughout the body, including the posterior cervical regions. Histologically, the enlarged nodes are flooded by atypical lymphocytes, with paracortical (T-cell) areas. Occasionally, cells resembling Reed-Sternberg cells, though lymphoma, are present. Because of these atypical features, special tests are some distinguish the reactive changes of mononucleosis from malignant lymphoma.

The **spleen** is enlarged in most cases, weighing between 300 and 500 gm. The histology is analogous to those of the lymph nodes, showing a heavy infiltration of atypical lymphocytes. The increase in splenic size and the infiltration of the trabeculae and capsule by the lymphocytes are fragile and prone to rupture after even minor trauma.

**Liver** function is almost always transiently impaired to some degree. Histologically, the changes are seen in the portal areas and sinusoids, and scattered, isolated cells or foci of atypical lymphocytes may be present. This histologic picture can be difficult to distinguish from viral hepatitis.

### *Clinical Course*



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Figure 12-12 Atypical lymphocytes in infectious mononucleosis. The cell on the left is a normal small lymphocyte with a small, round nucleus. In contrast, an atypical lymphocyte on the right has abundant, pale, foamy cytoplasm and a large, irregular, dark blue nucleus.

in contrast, an atypical lymphocyte on the right has abundant cytoplasm and a large nuclei

Although mononucleosis classically presents as fever, sore throat, lymphadenitis, and the other febrile presentations are not unusual. It can appear with little or no fever and only malaise, fatigue, and lymphadenitis; as a fever of unknown origin, unassociated with significant lymphadenopathy or other findings; or as a febrile illness that is difficult to differentiate from one of the hepatotropic viral syndromes ([Chapter 16](#)); or as a febrile illness with a rising titer of a capsid antigen, early antigen, or Epstein-Barr nuclear antigen. In most patients, mononucleosis is self-limiting, but sometimes the fatigue lasts longer. Occasionally, one or more complications supervene. Perhaps the most serious complication is hemophagocytic lymphohistiocytosis, associated with jaundice, elevated hepatic enzyme levels, disturbed appetite, and, rarely, death. Other complications involve the nervous system, kidneys, bone marrow, lungs, eyes, heart, and spleen.

EBV is a potent transforming virus that plays a role in a number of human malignancies, including nasopharyngeal carcinoma and nasopharyngeal lymphoma ([Chapter 6](#)). A serious complication in those lacking T-cell immunity (particularly organ and bone marrow transplant recipients) is EBV-driven B-cell proliferation that can run amok, leading to death. This process can be initiated by a reactivation of latent B-cell infection and generally begins as a polyclonal proliferation that progresses to overt malignancy. Reconstitution of immunity (e.g., by cessation of immunosuppressive therapy) is sometimes sufficient to halt the B-cell proliferation, which is uniformly fatal if left untreated.

The importance of T cells and NK cells in the control of EBV infection is driven home by X-linked lymphoproliferative disease, an inherited immunodeficiency characterized by inability to mount an immune response against EBV. In this disease, the *SH2D1A* gene, which encodes a signaling protein that is important in the activation of T cells, is mutated. More than 50% of these boys develop an overwhelming infection that is usually fatal. Of the remainder, who survive, they develop hypogammaglobulinemia, the basis of which is not understood.

### Reactive Lymphadenitis

Infections and nonmicrobial inflammatory stimuli not only cause leukocytosis but also involve the lymphatic system. Any immune response against foreign antigens is often associated with lymph node enlargement. Infections that cause lymphadenitis are numerous and varied and may be acute or chronic. In most cases, the response of the nodes is entirely nonspecific. A somewhat distinctive form of lymphadenitis that occurs with caseation is called tuberculous lymphadenitis.

### Acute Nonspecific Lymphadenitis

This form of lymphadenitis may be confined to a local group of nodes draining a focal infection, or it may be generalized, as in viral infections.

#### Morphology

Macroscopically, inflamed nodes in acute nonspecific lymphadenitis are swollen, grossly tender, and often covered by a fibrinous exudate. Histologically, there are **large germinal centers** containing numerous mitotic figures. If a pyogenic organism is present, a neutrophilic infiltrate is seen about the follicles and within the follicles. In severe infections, the centers of follicles can undergo necrosis, resulting in the formation of abscesses.

Affected nodes are tender and, when abscess formation is extensive, become fluctuant. The overlying skin is frequently red, and penetration of the infection to the skin can produce draining sinuses. If the infection is resolved, the lymph nodes can revert to their normal appearance or, if damaged by the infection, they can undergo scarring.

### Chronic Nonspecific Lymphadenitis

This condition can assume one of three patterns, depending on the causative agent: follicular hyperplasia, sinus histiocytosis, or follicular hyperplasia with sinus histiocytosis.

#### Morphology

**Follicular Hyperplasia.** This pattern is associated with infections or inflammatory stimuli that cause a reactive hyperplasia of the lymphoid tissue.

cells, which enter into B-cell follicles and create the **follicular (or germinal center)** reactive follicles include the activated B cells, scattered phagocytic macrophages (tingible body macrophages), and an inconspicuous meshwork of follicular dendritic antigen display to the B cells. Causes of follicular hyperplasia include **rheumatoid** and **the early stages of HIV infection**. This form of lymphadenitis can be confused with follicular lymphomas (discussed later). Findings that favor a diagnosis of follicular hyperplasia include (1) preservation of the lymph node architecture, with normal lymphoid tissue between follicles; (2) variation in the shape and size of the lymphoid nodules; (3) a mixed population of lymphocytes at all stages of differentiation; and (4) prominent phagocytic and mitotic activity in germinal centers.

**Paracortical Hyperplasia.** This pattern is characterized by reactive changes within the paracortex of the lymph node. On immune activation paracortical T cells transform into large proliferating lymphocytes that can efface the B-cell follicles. Paracortical hyperplasia is encountered in **viral infections** following certain **vaccinations** (e.g., smallpox), and in immune reactions induced by drugs (especially **phenytoin**<sup>®</sup>).

**Sinus Histiocytosis.** This reactive pattern is characterized by distention and proliferation of sinusoids, owing to a marked **hypertrophy of lining endothelial cells** and an infiltration of histiocytes. Sinus histiocytosis is often encountered in lymph nodes draining cancer, as part of the immune response to the tumor or its products.

### Cat Scratch Disease

Cat scratch disease is a self-limited lymphadenitis caused by the bacterium *Bartonella henselae*. Most of the patients are younger than 18 years of age. It presents as regional lymphadenopathy, most commonly of the upper extremities. Nodal enlargement appears approximately 2 weeks after a feline scratch or, uncommonly, after a bite. An inflammatory nodule, vesicle, or eschar is sometimes visible at the site of skin injury. In most patients, the disease regresses over the next 2 to 4 months. Rarely, patients develop encephalitis, osteomyelitis, or thrombocytopenia.

#### Morphology

The anatomic changes in the lymph node in cat scratch disease are quite characteristic. **Granulomas** are formed, but these then undergo central necrosis associated with infiltration by neutrophils. These **irregular stellate necrotizing granulomas** are similar in appearance to those seen in certain other infections, such as lymphogranuloma venereum. The microbe is extraorganismal and is visualized only with silver stains or electron microscopy. The diagnosis is based on exposure to cats, the clinical findings, a positive skin test to the microbial antigen, and the distinctive changes in the lymph nodes.







## NEOPLASTIC PROLIFERATIONS OF WHITE CELLS

Tumors represent the most important of the white cell disorders. They can be divided into three broad categories: lymphoid neoplasms, myeloid neoplasms, and histiocytic neoplasms.

*Lymphoid neoplasms*, which include non-Hodgkin lymphomas (NHLs), Hodgkin lymphoma, and plasma cell dyscrasias and related disorders. In many instances these tumors are composed of cells that are arrested at various stages of lymphocyte differentiation, a feature that serves as one of the bases for their classification. *Myeloid neoplasms* include acute and chronic leukemias, which normally give rise to the formed elements of the blood: granulocytes, red cells, and platelets. They can be divided into three fairly distinct subcategories: *acute myelogenous leukemias*, in which immature progenitor cells proliferate in the bone marrow; *chronic myeloproliferative disorders*, in which inappropriately increased production of mature myeloid cells leads to elevated blood cell counts; and *myelodysplastic syndromes*, which are characterized by dysplasia of one or more myeloid lineages and cytopenias. *Histiocytic neoplasms* represent proliferative lesions of histiocytes. Of special importance are the *Langerhans cell histiocytoses*, which comprise a group of disorders involving Langerhans cells (the *Langerhans cell histiocytoses*).

### Lymphoid Neoplasms

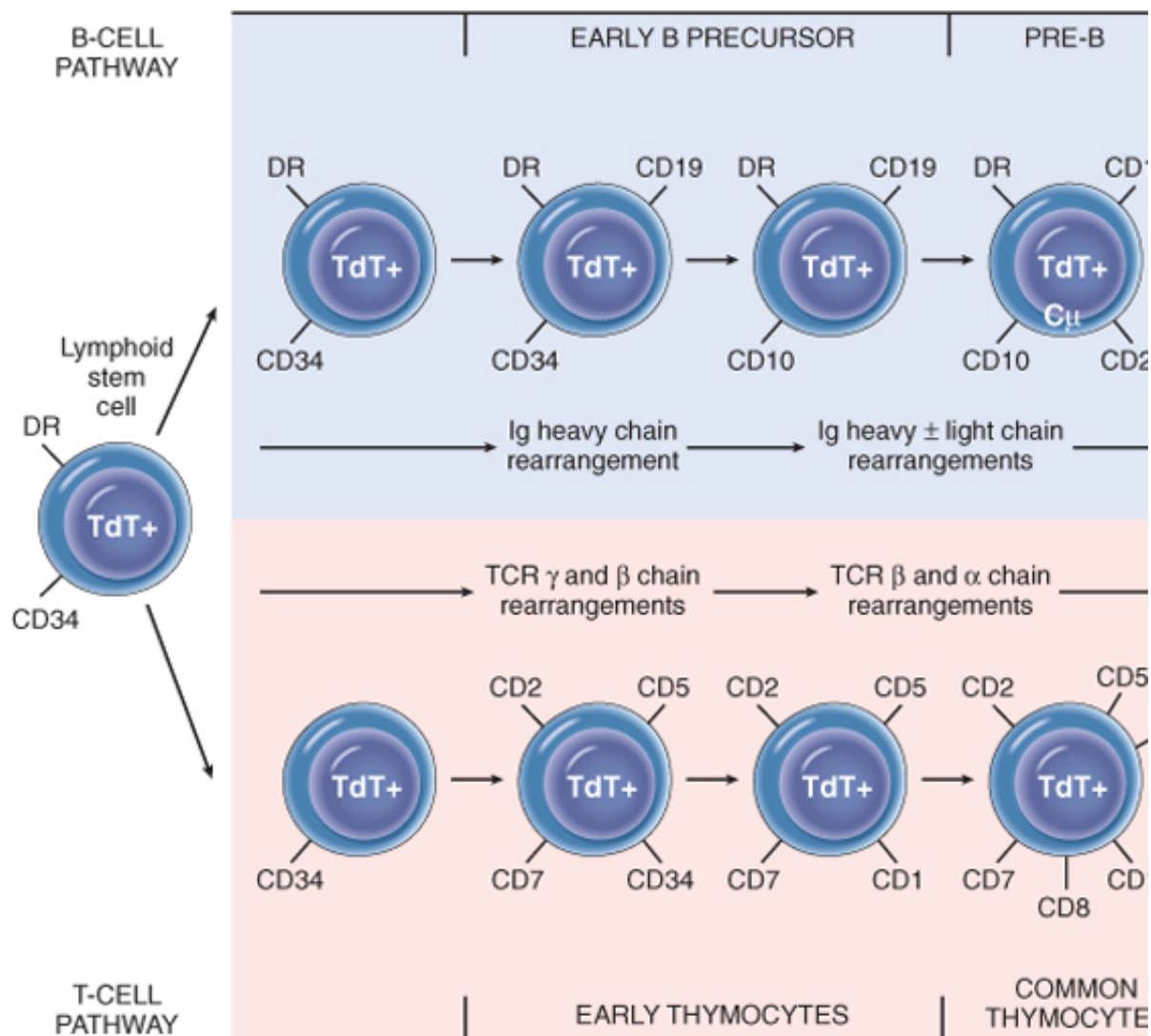
The lymphoid neoplasms encompass a group of entities that vary widely in their clinical presentation and pathogenesis. Some of these neoplasms characteristically appear as masses in the bone marrow with spillage of neoplastic cells into the peripheral blood. Others tend to present as discrete masses in involved lymph nodes or other tissues. Plasma cell tumors, the *plasma cell dyscrasias*, are discrete masses and cause systemic symptoms related to the production of a complete or partial paraprotein. In all these tendencies, all lymphoid neoplasms have the potential to spread to lymph nodes and various other organs, including the liver, spleen, and bone marrow. In some cases lymphomas or plasma cell tumors spill over into the peripheral blood, creating a leukemia-like picture. Conversely, leukemias of lymphoid cells, originating in the bone marrow, can create the histologic picture of lymphoma. *Because of the overlap in clinical presentations, the various lymphoid neoplasms are distinguished based on the appearance and molecular characteristics of the tumor cells.* Stated another way, for prognostication, it is most helpful to focus on what the tumor cell is, not where it resides in the patient.

Two groups of lymphomas are recognized: Hodgkin lymphoma and non-Hodgkin lymphomas. Although both arise from lymphoid tissues, Hodgkin lymphoma is set apart by the presence of distinctive neoplastic Reed-Sternberg cells. In non-Hodgkin lymphomas, the involved nodes are usually greatly outnumbered by non-neoplastic inflammatory cells. The biological behavior of Hodgkin lymphoma is also different from those of most NHLs, making the distinction of practical importance.

Historically, few areas of pathology have evoked as much controversy and confusion as the classification of lymphoid neoplasms, perhaps inevitable given the intrinsic complexity of the immune system from which they arise. Over the past decade in this area, however, and an international working group of pathologists, molecular biologists, and hematologists, the World Health Organization (WHO) has formulated a widely accepted classification scheme that integrates morphologic, phenotypic, genotypic, and clinical features. Before we delve into the classification of lymphoid neoplasms, the principles that should be emphasized:

B- and T-cell tumors are often composed of cells that are arrested or derived from specific pathways (Fig. 12-13). The diagnosis and classification of these tumors relies heavily on techniques (e.g., flow cytometry) that detect lineage-specific antigens (e.g., B-cell, T-cell, and NK-cell markers). As is evident, many such markers are identified according to their cluster of differentiation (CD) number. In adults, B-cell lymphomas are derived from follicular center or post-follicular center B cells. This conclusion is based on the fact that most B-cell lymphomas have undergone somatic hypermutation, an activity characteristic of follicular center B cells. Follicular center B cells also undergo immunoglobulin class switching, and together with the presence of regulated genomic instability seem to place B cells at a relatively high risk for mutations. Many recurrent chromosomal translocations that are commonly seen in mature B-cell malignancies

many recurrent chromosomal translocations that are commonly seen in mature B-cell malignancies and seem to stem from mistakes that are made during attempted recombination events. It is interesting that mature T cells (which are genomically stable) give rise to lymphomas with many chromosomal translocations involving the T-cell receptor loci. All lymphoid neoplasms are clonal and are therefore monoclonal. As will be recalled from Chapter 5, during the differentiation of pre-B and T cells, there is a rearrangement of their antigen receptor genes. This process ensures that each lymphocyte expresses a unique antigen receptor. Because antigen receptor gene rearrangement precedes transformation, the daughter cells of a single progenitor share the same antigen receptor gene configuration and synthesize identical antibodies (or immunoglobulins or T-cell receptors). For this reason, *analysis of antigen receptor genes is used to differentiate monoclonal neoplasms from polyclonal, reactive processes*. As tumors progress, neoplasms often disrupt normal immune regulatory mechanisms. Both immunodeficiency (e.g., HIV infection) and autoimmunity can be seen, sometimes in the same patient. Ironically, patients with immunodeficiency are themselves at high risk of developing certain lymphoid neoplasms, particularly B-cell lymphoma. Although NHLs often present at a particular tissue site, sensitive molecular assays can detect disseminated disease at the time of diagnosis. As a result, with few exceptions, only systemic therapy is effective. Lymphoma often presents at a single site and spreads in a predictable fashion to contiguous sites. If detected early in its course, local therapy may be indicated.



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Figure 12-13 Origin of lymphoid neoplasms. Stages of B- and T-cell differentiation from which specific lymphoid  
differentiation: DR, human lymphocyte antigen-class II antigens; Ig, immunoglobulin; TCR, T-cell receptor; Td

differentiation, DR, human lymphocyte antigen-class II antigens, Ig, immunoglobulin, TCR, T-cell receptor, Td

The WHO classification of lymphoid neoplasms considers the morphology, cell of origin (determined by immunophenotype), clinical features, and genotype (e.g., karyotype, presence of viral genomes) of each entity. It includes acute lymphoblastic leukemia, multiple myeloma, and segregates them on the basis of origin into three major categories: (1) B-cell lymphomas, (2) T-cell lymphomas, and (3) Hodgkin lymphoma.

An updated version of the WHO classification of lymphoid neoplasms is presented in Table 12-7. There are numerous. Our focus will be on the subset of neoplasms listed below, which together constitute the most common lymphoid neoplasms seen in the United States:

Precursor B- and T-cell lymphoblastic leukemia/lymphoma (commonly called acute lymphoblastic leukemia)  
 B-cell lymphoma/chronic lymphocytic leukemia  
 Follicular lymphoma  
 Mantle cell lymphoma  
 Burkitt lymphoma  
 Multiple myeloma and related plasma cell dyscrasias  
 Hodgkin lymphoma

The salient features of the more common lymphoid neoplasms are summarized in Table 12-8. We will also discuss some uncommon entities that have distinctive clinicopathologic features.

### **Precursor B- and T-Cell Lymphoblastic Leukemia/Lymphoma**

These are aggressive tumors, composed of immature lymphocytes (lymphoblasts), which occur primarily in children. The various lymphoblastic tumors are morphologically indistinguishable and often cause similar clinical features. Because precursor B- and T-cell neoplasms have overlapping features, we will consider them together.

**Table 12-7. The WHO Classification of Lymphoid Neoplasms\***

<b>Precursor B-Cell Neoplasms</b>
<i>Precursor B-cell leukemia/lymphoma (B-cell ALL)</i>
<b>Peripheral B-Cell Neoplasms</b>
<i>B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL)</i>
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
<i>Mantle cell lymphoma</i>
<i>Follicular lymphoma</i>
<i>Extranodal marginal zone lymphoma (MALT lymphoma)</i>
Splenic marginal zone lymphoma
Nodal marginal zone lymphoma
Hairy cell leukemia
<i>Plasmacytoma/plasma cell myeloma</i>
<i>Diffuse large B-cell lymphoma</i>
<i>Burkitt lymphoma</i>
<b>Precursor T-Cell Neoplasms</b>
<i>Precursor T-cell leukemia/lymphoma (T-cell ALL)</i>
<b>Peripheral T-/NK-Cell Neoplasms</b>
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
<i>Mycosis fungoides/Sézary syndrome</i>
<i>Peripheral T-cell lymphoma, not otherwise specified (NOS)</i>
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, primary systemic type
Enteropathy-type T-cell lymphoma

Panniculitis-like T-cell lymphoma
Hepatosplenic $\gamma\delta$ T-cell lymphoma
Adult T-cell lymphoma/leukemia (HTLV1)
NK/T-cell lymphoma, nasal type
NK-cell leukemia
<b>Hodgkin Lymphoma</b>
Lymphocyte predominance, nodular
<i>Nodular sclerosis</i>
<i>Mixed cellularity</i>
Lymphocyte-rich
Lymphocyte depletion

\*Entries in italics are among the most common lymphoid tumors.

Just as B-cell precursors normally develop within the bone marrow, pre-B-lymphoblastic tumors circulate in the peripheral blood as leukemias. Similarly, pre-T-lymphoblastic tumors commonly present as marrow-based tumors at early stages of normal T-cell differentiation. However, pre-T-cell "lymphomas" often progress to leukemia. pre-T-cell tumors seem to involve only the marrow at presentation. Hence, *both pre-B- and pre-T-cell lymphomas have the clinical appearance of an acute lymphoblastic leukemia (ALL) at some time during their course.* Acute lymphoblastic leukemia (ALL) is a childhood leukemia, peaking in incidence at age 4, with most of the cases being of pre-B-cell origin. It is also common in adolescent males of between 15 and 20 years of age.

The pathophysiology, laboratory findings, and clinical features of ALL closely resemble those of other major types of acute leukemia. Because of these similarities, we will first step back to review leukemias before discussing those that are specific to ALL.

#### *Pathophysiology of Acute Leukemias*

Although acute leukemias are rapidly growing tumors, normal bone marrow progenitors grow at a normal rate. *A pathogenetic problem in acute leukemia is a block in differentiation.* This leads to the accumulation of immature cells in the marrow, which suppress the function of normal hematopoietic stem cells by physical displacement and by inhibitory mechanisms. Eventually bone marrow failure results, which accounts for the major clinical manifestations. The therapeutic goal is to reduce the leukemic clone sufficiently to allow normal hematopoiesis to resume.

#### *Clinical Features of Acute Leukemias*

The acute leukemias have the following characteristics:

*Abrupt stormy onset.* Most patients present within 3 months of the onset of symptoms. *Symptoms include fatigue* (due mainly to anemia), *fever* (reflecting infections), *leukocytosis* (due to leukocytes), and *bleeding* (petechiae, ecchymoses, epistaxis, gum bleeding) secondary to *thrombocytopenia*. These result from marrow expansion and infiltration of the subperiosteum. *Gross splenomegaly, and hepatomegaly.* These reflect dissemination of the leukemic cells, and are more common in AML. *Central nervous system manifestations.* These include headache, vomiting, and nerve root pain; these features are more common in children than in adults and are more common in AML.

#### *Laboratory Findings of Acute Leukemias*

The diagnosis of acute leukemia rests on the identification of blast forms in the peripheral blood and bone marrow. The white blood cell count is variable; it is sometimes elevated to more than 100,000 cells/ $\mu$ L, but in about 50% of patients it is normal. Hemoglobin is almost always present, and the platelet count is usually below 100,000 platelets/ $\mu$ L. Neutropenia is common in the blood. Uncommonly the peripheral blood examination shows pancytopenia but no blasts (aleukemic presentation); this can only be established by examining the bone marrow.

#### **Morphology**

**Because of different responses to therapy, it is of great practical importance to distinguish between AML and ALL.** By definition, in ALL, blasts compose more than 25% of the marrow cellularity.



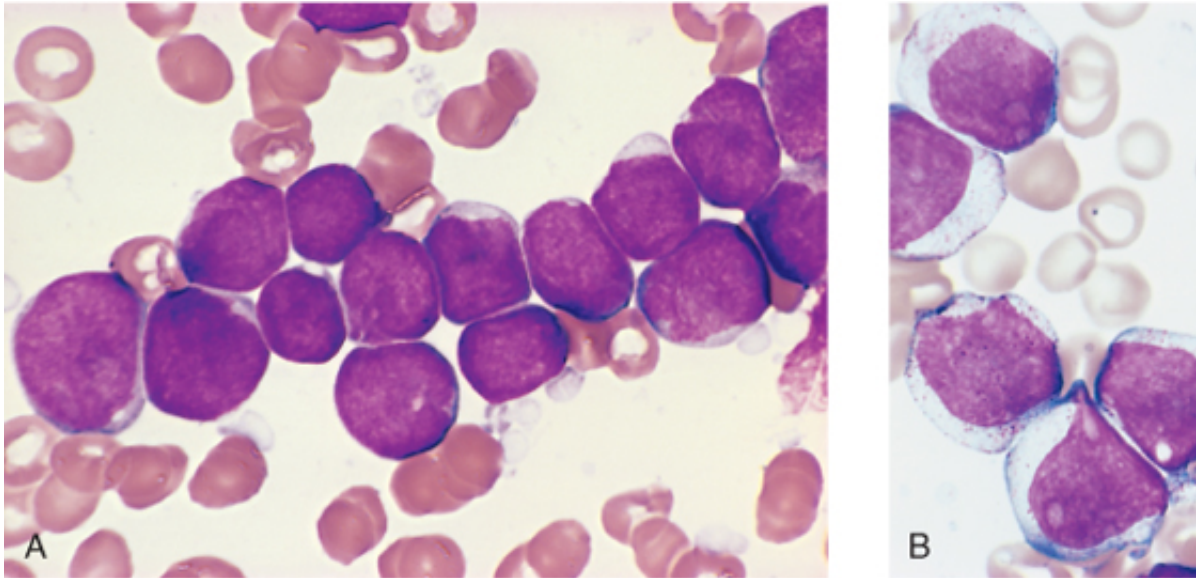
lymphoblasts in Wright-Giemsa-stained preparations have somewhat coarse and one or two nucleoli (Fig. 12-14A); myeloblasts tend to have finer chromatin and may contain granules (Fig. 12-14B). The cytoplasm of lymphoblasts often contains large acid-Schiff-positive material, whereas myeloblasts are often peroxidase positive.

**Table 12-8. Summary of the More Common Lymphoid Neoplasms**

Entity	Frequency	Salient Morphology	Immunophenotype	Comments
<b>Precursor B-cell lymphoblastic leukemia/lymphoma</b>	85% of childhood acute leukemia	Lymphoblasts with irregular nuclear contours, condensed chromatin, small nucleoli, and scant agranular cytoplasm	TdT+immature B cells (CD19+, variable expression of other B-cell markers)	Usual precursor of B-cell lymphoma
<b>Precursor T-cell leukemia/lymphoma</b>	15% of childhood acute leukemia; 40% of childhood lymphomas	Identical to precursor B-cell lymphoblastic leukemia/lymphoma	TdT+immature T cells (CD2+, CD7+, variable expression of other T-cell markers)	More common in males
<b>Small lymphocytic lymphoma/chronic lymphocytic leukemia</b>	3% to 4% of adult lymphomas; 30% of all leukemias	Small resting lymphocytes mixed with variable numbers of large activated cells; lymph nodes diffusely effaced	CD5+B-cell expressing surface Ig	Occurs in older patients
<b>Follicular lymphoma</b>	40% of adult lymphomas	Frequent small "cleaved" cells mixed with large cells; growth pattern is usually nodular (follicular)	CD10+BCL2+mature B cells that express surface Ig	Occurs in older patients with nodular growth
<b>Mantle cell lymphoma</b>	3% to 4% of adult lymphomas	Small to intermediate-sized irregular lymphocytes growing in a diffuse pattern	CD5+mature B cells that express cyclin D1 and have surface Ig	Occurs in older patients with nodular growth
<b>Extranodal marginal zone lymphoma</b>	~5% of adult lymphomas	Variable cell size and differentiation; 40% show plasmacytic differentiation; B cells home to epithelium, creating "lymphoepithelial lesions"	CD5- CD10- mature B cells with surface Ig	Frequently involves extranodal sites
<b>Diffuse large B-cell lymphoma</b>	40% to 50% of adult lymphomas	Variable; most resemble large germinal center B cells; diffuse growth pattern	Mature B cells with variable expression of CD10 and surface Ig	Occurs in older patients with aggressive growth
<b>Burkitt lymphoma</b>	<1% of lymphomas in the United States	Intermediate-sized round lymphoid cells with several nucleoli; diffuse tissue involvement associated with apoptosis produces a "starry-sky" appearance	Mature CD10+B cells expressing surface Ig	Encapsulated; often high-grade
<b>Plasmacytoma/plasma cell myeloma</b>	Most common lymphoid neoplasm in older adults	Plasma cells in sheets, sometimes with prominent nucleoli or inclusions containing Ig	Terminally differentiated plasma cells containing cytoplasmic Ig	Myeloid; disseminated; hypercalcemia; bone disease
<b>Mycosis fungoides</b>	Most common cutaneous lymphoid malignancy	In most cases, small lymphoid cells with markedly convoluted nuclei; cells often infiltrate the epidermis (Pautrier microabscesses)	CD4+mature T cells	Preferential skin involvement; Sézary syndrome
<b>Peripheral T-cell lymphoma, not otherwise specified (NOS)</b>	Most common adult T-cell lymphoma	Variable; usually a spectrum of small to large lymphoid cells with irregular nuclear contours	Mature T-cell phenotype (CD3+)	Protruding; aggressive
<b>Hodgkin lymphoma, nodular sclerosis type</b>	Most common type of Hodgkin	Lacunar Reed-Sternberg cell variants in a mixed inflammatory background; broad sclerotic bands	CD15+, CD30+Reed-Sternberg cells	Most common in females

	Hodgkin lymphoma	background, broad sclerotic bands of collagen usually also present		
<b>Hodgkin lymphoma, mixed cellularity type</b>	Second most common form of Hodgkin lymphoma	Frequent classic Reed-Sternberg cells in a mixed inflammatory background	CD15+, CD30+Reed-Sternberg cells	More frequent in males

GI, gastrointestinal; Ig, immunoglobulin.



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Figure 12-14 Morphologic comparison of lymphoblasts and myeloblasts. **A**, Lymphoblastic leukemia/lymphoma: myeloblasts, and the nuclear chromatin is more condensed. Cytoplasmic granules are absent. **B**, Acute myeloblastic leukemia: delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm. (Courtesy of Dr. F. F. University of Texas Southwestern Medical School, Dallas, Texas.)

Having completed our "short course" in acute leukemia, we will return to lymphoblastic leukemia/lymphoma.

### Immunophenotyping

Immunophenotyping is very useful in subtyping lymphoblastic tumors and distinguishing them from other types. One enzyme that is specifically expressed in pre-B and pre-T cells, is present in more than 95% of cases. For B-cell types, this enzyme is CD19 (B cell) and for T-cell types, it is CD3. The presence of these markers has historically proven somewhat useful in predicting clinical outcome, the tumor karyotype provides additional information.

### Karyotypic Changes

Approximately 90% of patients with lymphoblastic leukemia/lymphoma have nonrandom karyotypic changes. The most common is hyperdiploidy (>50 chromosomes/cell), which is associated with the presence of a chromosome 12 abnormality involving the *TEL1* and *AML1* genes. The presence of these aberrations correlates with a good outcome for pre-B-cell tumors that have translocations involving the *MLL* gene on chromosome 11q23 or the *F* gene. For T-cell tumors, the presence of these aberrations is not predictive of outcome.

### Activating Mutations in *NOTCH1*

*NOTCH1* is a transmembrane receptor whose activity is essential for normal T-cell development. It promotes proliferation and survival of pre-T cells and is capable of causing stem cells to differentiate into T cells. Interestingly, 55% to 60% of pre-T-cell tumors have activating point mutations in *NOTCH1*, indicating that it plays a central role in the development of many pre-T ALLs. The ability of *NOTCH1* to promote T-cell development is a key feature of its function.

explain why some patients with pre-T-cell tumors have bone marrow disease and no thymic involvement.

### *Prognosis*

Treatment of lymphoblastic tumors of childhood represents one of the great success stories in oncology. Most patients have the best prognosis; most can be cured. Other groups of patients do less well. Variables correlating with outcome include gender, age younger than 2 or older than 10 years, and a high leukocyte count at diagnosis. Age-related chromosomal abnormalities are likely to explain the relationship of age to outcome. Tumor chromosomes (both associated with a poor outcome) are most common in children younger than 2 years. Tumor chromosomes with "good prognosis" chromosomal aberrations (such as the t[12;21] and hyperdiploidy) are most common in older children.

### **Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia**

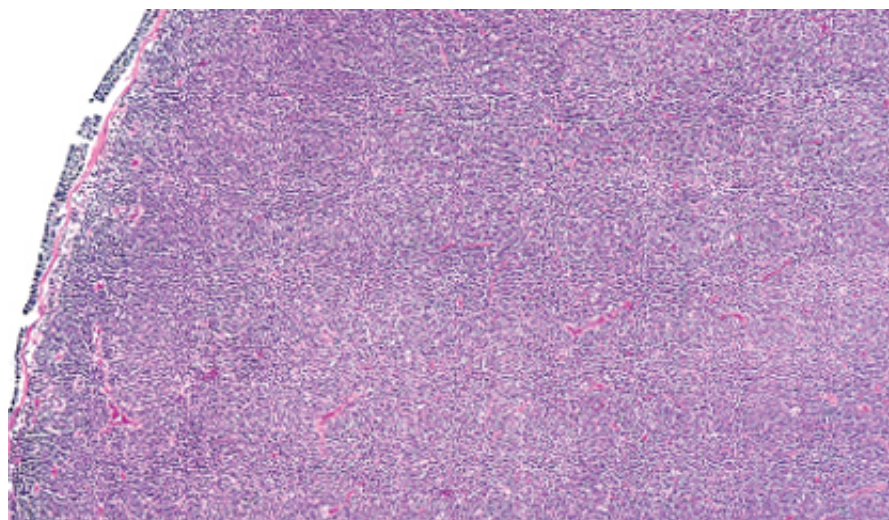
These two disorders are morphologically, phenotypically, and genotypically identical, differing only in site of involvement. Arbitrarily, if the peripheral blood lymphocytosis exceeds 4000 cells/mm<sup>3</sup>, the patient has chronic lymphocytic leukemia (CLL); if not, a diagnosis of small lymphocytic lymphoma (SLL) is made. Most patients fit the definition of a common leukemia of adults in the western world. In contrast, SLL constitutes only 4% of NHLs. CLL is much less common in Asia.

### *Pathophysiology*

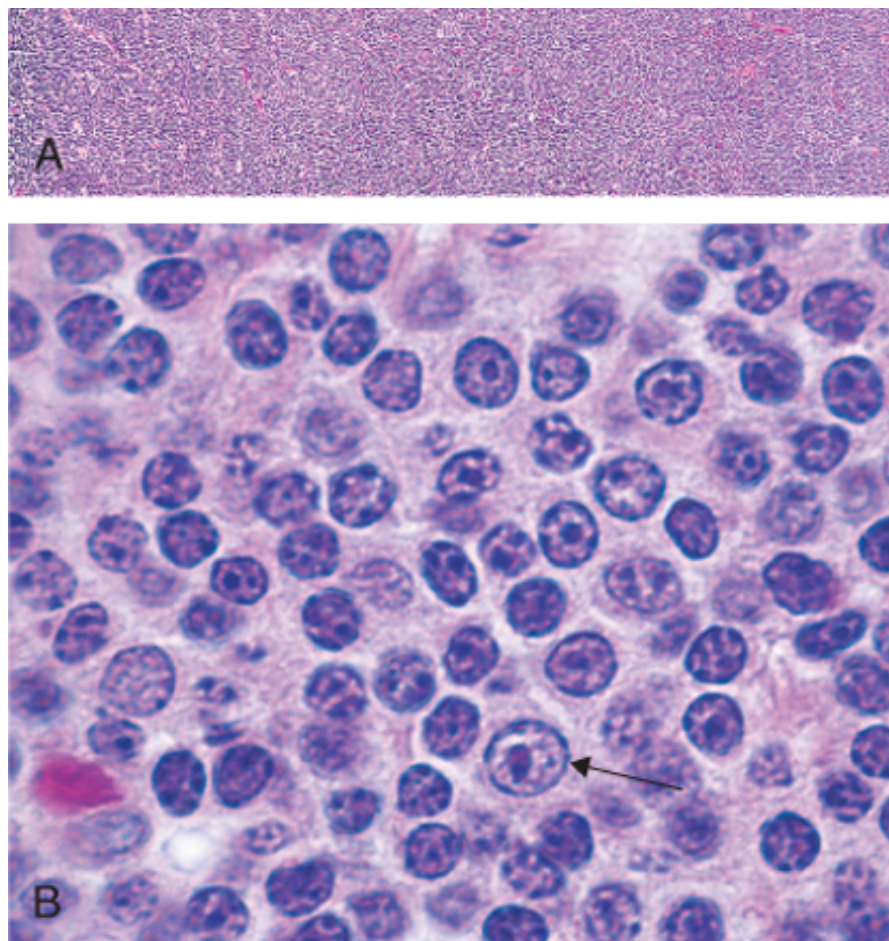
The neoplastic B cells, through mechanisms that are not understood, suppress normal B-cell function, leading to hypogammaglobulinemia. Paradoxically, approximately 15% of patients have autoantibodies against red blood cells; autoantibodies can also be detected. When present, these autoantibodies are made by nontumor B cells. Breakdown in immune regulation. As time passes the tumor cells tend to displace the normal marrow cells, leading to neutropenia, and eventual thrombocytopenia.

### **Morphology**

In SLL/CLL, sheets of small round lymphocytes and scattered ill-defined foci of larger cells diffusely efface involved lymph nodes (Fig. 12-15A). The predominant cells are small lymphocytes with dark-staining round nuclei, scanty cytoplasm, and little variation in size. Foci of mitotically active cells are called **proliferation centers**; their presence is pathognomonic. Mitotic figures are rare except in the proliferation centers, and there is little or no cytoplasm. Involvement of the lymph nodes, the bone marrow, spleen, and liver are involved in almost all cases. There is an **absolute lymphocytosis** of small, mature-looking lymphocytes. The neoplastic cells are fragile and are frequently disrupted during the preparation of smears, which produces **smudged cells**. Variable numbers of larger activated lymphocytes are also usually present in







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 Figure 12-15 Nodal involvement by small lymphocytic lymphoma/chronic lymphocytic leukemia. **A**, Low-power view  
**B**, At high power, the majority of the tumor cells have the appearance of small, round lymphocytes. A single "pro"  
 nucleolus, is also present in this field. (**A**, Courtesy of Dr. José Hernandez, Department of Pathology, University of  
 Texas.)

#### *Immunophenotype, Karyotype, and Molecular Features*

CLL/SLL is a neoplasm of mature B cells expressing the pan-B-cell markers CD19, CD20, and CD22 and light chains. The tumor cells also express CD5, a tendency that is shared (among the B-cell r Approximately 50% of patients have karyotypic abnormalities, the most common of which are trisomy 12 and 13. Unlike other lymphoid neoplasms, chromosomal translocations are rare. Of interest, most have hypermutation of their immunoglobulin segments, a finding that is consistent with an origin from a memory cell). Less commonly these tumors are derived from naive B cells that have not undergone somatic hypermutation; these appear to have a substantially worse prognosis.

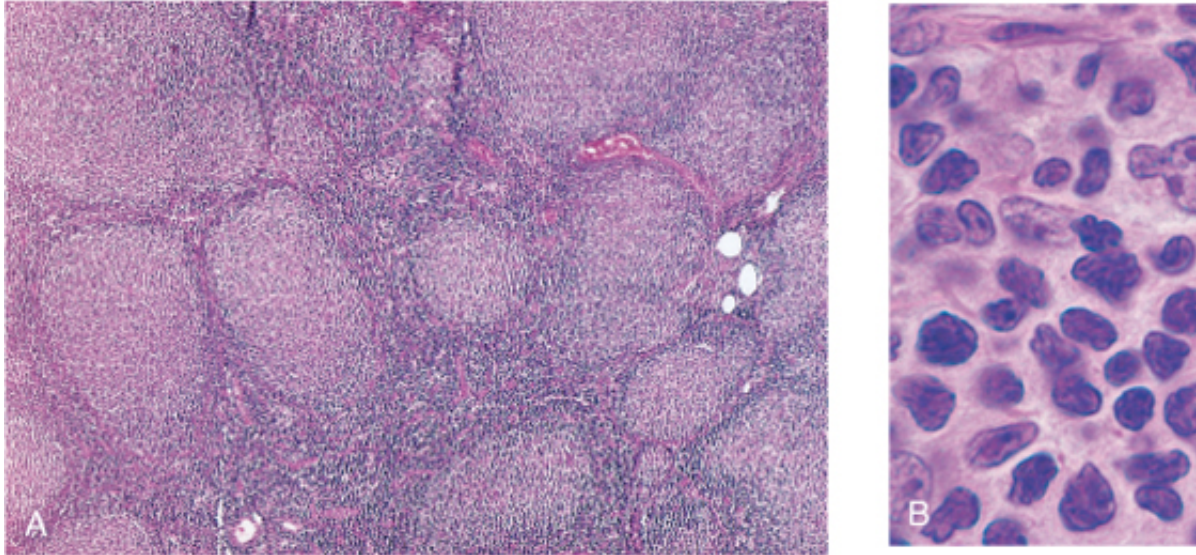
#### *Clinical Features*

CLL/SLL is often asymptomatic at presentation. The most common symptoms are nonspecific and include fatigue, weight loss, and anorexia. Generalized *lymphadenopathy* and *hepatosplenomegaly* are present in 50% to 60% of patients. Lymphocyte counts may be increased only slightly (in SLL) or may exceed 200,000 cells/ $\mu$ L. *Hypogammaglobulinemia* develops usually late in the course of the disease, and is responsible for increased susceptibility to bacterial infections. *Hemolytic anemia* and *thrombocytopenia* are seen. The course and prognosis are extremely variable. Some patients survive many years after diagnosis and die of unrelated causes; the median survival is 4 to 6 years. However, a subset of patients transform to more aggressive tumors that resemble either pro-lymphocytic leukemia or diffuse large B-cell lymphoma; if this occurs, the median survival is less than 1 year.



### **Follicular Lymphoma**

These are relatively common tumors that constitute 40% of the adult NHLs in the United States. Lymphoma is frequently in Asian populations.



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Figure 12-16 Follicular lymphoma, involving a lymph node. **A**, Nodular aggregates of lymphoma cells are present. **B**, The tumor cells resemble normal follicular center B cells. Most commonly, the predominant cells are "centrocyte-like" cells slightly larger than resting lymphocytes that have angular nuclear contours with prominent indentations and linear infoldings (see Fig. 12-16B). The nuclei are condensed, and nucleoli are indistinct. These small, cleaved cells are mixed with larger "centroblast-like" cells that have vesicular chromatin, several nucleoli, and more cytoplasm. In most tumors, centroblast-like cells are a minor component of the overall population. Infrequent, and single necrotic cells (cells undergoing apoptosis) are not seen. The distinction between neoplastic follicles and reactive follicles, in which mitoses and apoptotic cells are seen, is often difficult. Uncommonly, centroblast-like cells predominate, a histology that correlates with a more aggressive clinical behavior.

### **Morphology**

Lymph nodes are effaced by proliferations that usually have a distinctly **nodular architecture**. The tumor cells resemble normal follicular center B cells. Most commonly, the predominant cells are "centrocyte-like" cells slightly larger than resting lymphocytes that have angular nuclear contours with prominent indentations and linear infoldings (see Fig. 12-16B). The nuclei are condensed, and nucleoli are indistinct. These small, cleaved cells are mixed with larger "centroblast-like" cells that have vesicular chromatin, several nucleoli, and more cytoplasm. In most tumors, centroblast-like cells are a minor component of the overall population. Infrequent, and single necrotic cells (cells undergoing apoptosis) are not seen. The distinction between neoplastic follicles and reactive follicles, in which mitoses and apoptotic cells are seen, is often difficult. Uncommonly, centroblast-like cells predominate, a histology that correlates with a more aggressive clinical behavior.

### **Immunophenotype and Molecular Features**

These tumors express the pan-B-cell markers CD19 and CD20, CD10, and BCL6, a transcription factor involved in B-cell development. In addition, the neoplastic cells characteristically express BCL2, a protein that is absent in normal follicular center B cells. As would be expected of a B cell-derived tumor, the immunoglobulin genes show evidence of somatic hypermutation.

### **Karyotype**

The majority of tumors have a characteristic t(14;18) translocation. This translocation fuses the BCL2 gene on chromosome 18 with the IgH locus on chromosome 14 and leads to the inappropriate expression of BCL2 protein, which functions as an anti-apoptotic factor.

### **Clinical Features**

Follicular lymphoma occurs predominantly in older persons (rarely before age 20 years) and affects both sexes. It presents as *painless lymphadenopathy*, which is frequently generalized. Involvement of visceral organs is uncommon. The disease *almost always contains lymphoma* at the time of diagnosis. The natural history is prolonged (median survival is 8-12 years).

*lymphoma is not easily curable*, a feature that is common to most of the indolent lymphoid malignancies. In part, this is due to the elevated levels of BCL2, which may protect tumor cells from the effects of chemotherapy. In some cases, follicular lymphoma progresses to a diffuse large B-cell lymphoma, with or without treatment. These lymphomas arising from such conversions are much less curable than de novo diffuse large B-cell lymphomas.

### **Mantle Cell Lymphoma**

Mantle cell lymphomas are composed of B cells that resemble cells in the mantle zone of normal lymphoid follicles. They account for approximately 4% of all NHLs and occur mainly in older males.

#### **Morphology**

Mantle cell lymphomas involve lymph nodes in a diffuse or vaguely nodular pattern. The tumor cells are usually slightly larger than normal lymphocytes and have an irregular nucleus and scant cytoplasm. Less commonly, the cells are larger and morphologically resemble lymphoblasts. Tumor cells are typically involved in the majority of cases, and about 20% of patients have peripheral blood involvement. A characteristic tendency is the frequent involvement of the gastrointestinal tract, often in the form of multifocal submucosal nodules that grossly resemble polyps (lymphomatous polyposis).

#### **Immunophenotype**

The tumor cells usually coexpress surface IgM and IgD, the pan-B-cell antigens CD19 and CD20, and the B-cell marker CD22. Mantle cell lymphoma is distinguished from CLL/SLL by the absence of proliferation centers and the presence of a t(11;14) translocation.

#### **Karyotype and Molecular Features**

Most (and possibly all) tumors have a t(11;14) translocation that fuses the cyclin D1 gene on chromosome 12 with the IgH locus on chromosome 14. This translocation dysregulates the expression of cyclin D1, a cell cycle regulator, leading to characteristically increased cyclin D1 protein levels. The immunoglobulin loci have not undergone a clonal rearrangement, consistent with an origin from a naive B cell.

#### **Clinical Features**

Most patients present with fatigue and lymphadenopathy and are found to have generalized disease involving the lymph nodes, spleen, liver, and (often) the gastrointestinal tract. These tumors are aggressive and incurable, and are associated with a median survival of 3 to 5 years.

### **Diffuse Large B-Cell Lymphoma**

This diagnostic category includes several forms of NHL that share certain features, including a B-cell phenotype, a diffuse growth pattern, and an aggressive clinical history. As a group, *this is the most important type of lymphoma in adults*.

#### **Morphology**

The nuclei of the neoplastic B cells are large (at least three to four times the size of normal lymphocytes) and can take a variety of forms. In many tumors, cells with round, irregular, or cleaved nuclei and dispersed chromatin, several distinct nucleoli, and modest amounts of pale cytoplasm are seen (Figure 17-17). Such cells resemble "centroblasts," the large cells that are seen in reactive lymphoid follicles. In other tumors, the cells have a large round or multilobulated vesicular nucleus, one or two prominent nucleoli, and abundant cytoplasm that can be either pale or intensely stained. These cells resemble an "immunoblast," a type of antigen-activated lymphocyte that is normally found in the germinal centers of lymph nodes.

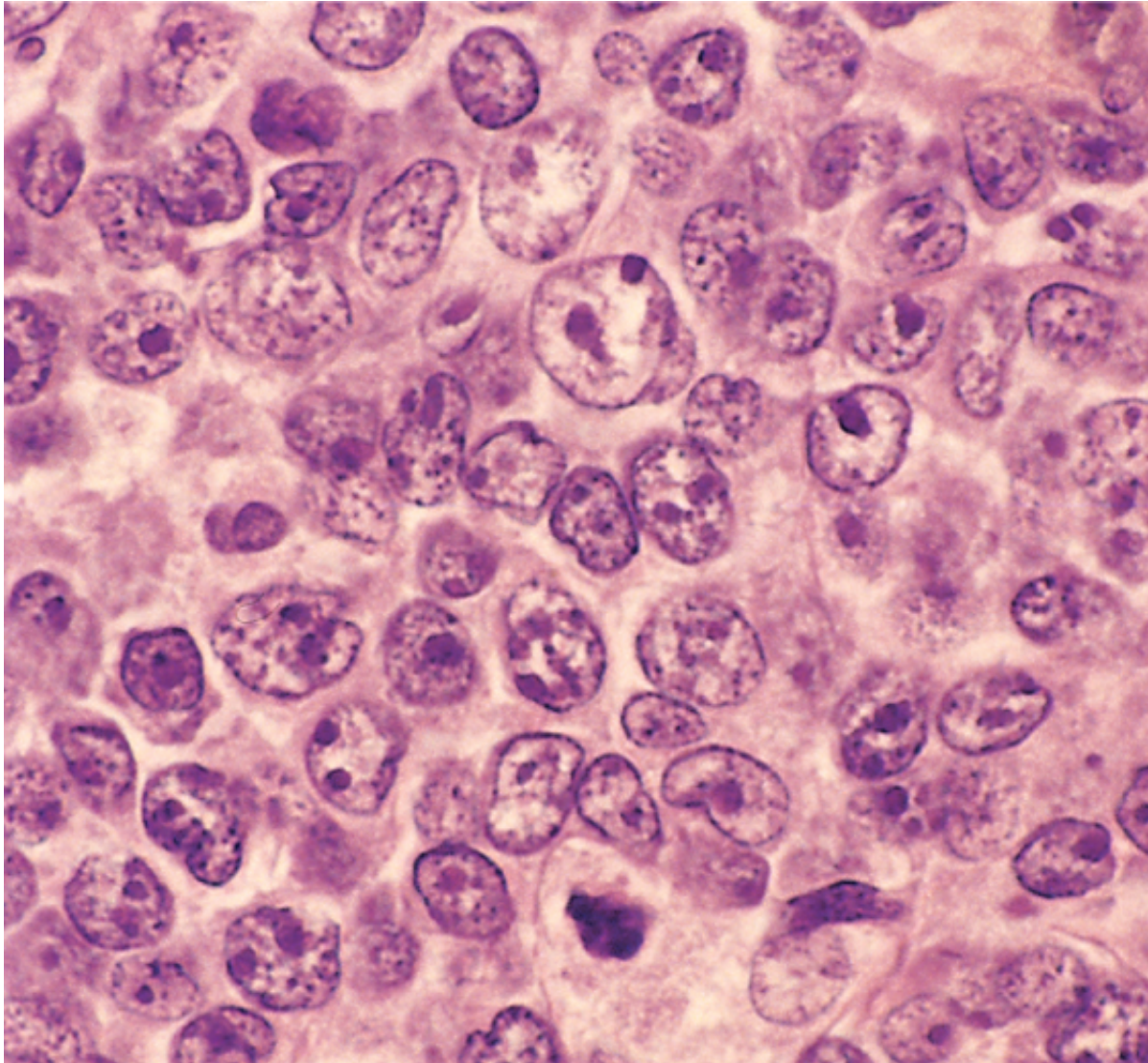
#### **Immunophenotype and Molecular Features**

These are mature B-cell tumors that express pan-B-cell antigens, such as CD19 and CD20. Many other antigens (e.g., CD10) are variably expressed. These tumors uniformly demonstrate somatic hypermutation of the immunoglobulin loci, consistent with an origin from a follicular or post-follicular center B cell.

### Karyotype

Approximately 30% of tumors have a t(14;18) translocation involving the *BCL2* gene. Such tumors are called follicular lymphomas. About one-third have rearrangements of the *BCL6* gene, located on 3q27, and mutations of the *MYD88* gene, located on 2p16, in a small fraction of tumors. Both the translocations and the mutations seem to cause inappropriate increases in cell survival.

### Distinct Subtypes



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Figure 12-17 Diffuse large B-cell lymphoma. The tumor cells have large nuclei with open chromatin and prominent nucleoli. (H&E, ×1000)  
Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas

Several distinctive clinicopathologic subtypes are included in the general category of diffuse large B-cell lymphomas that arise in the setting of the acquired immunodeficiency syndrome (AIDS). In the post-transplant setting, these tumors are polyclonal B-cell proliferations that may regress if immune function is restored. Otherwise, with time, the lymphoma progresses. *Kaposi sarcoma herpesvirus (KSHV)*, also called *human herpesvirus type 8*, is a member of the *gamma-2* group of tumors that present as *primary effusion lymphomas* within the pleura, pericardium, or peritoneum. These lymphomas are usually immunosuppressed. Note that this virus is also associated with K



children lymphomas are usually immunosuppressed. Note that this virus is also associated with HL (Fig. 12-5). **Mediastinal large B-cell lymphoma** usually presents in young females and shows a predilection for the central nervous system.

### *Clinical Features*

Although the median age at presentation is about 60 years, diffuse large B-cell lymphomas can arise at any age, including childhood lymphomas. Patients typically present with a rapidly enlarging, often symptomatic mass. Extranodal presentations are common. Although the gastrointestinal tract and the brain are among the more common sites, lymphomas can arise in virtually any organ or tissue. Unlike the more indolent lymphomas (e.g., follicular lymphoma), bone marrow involvement is not common at the time of diagnosis.

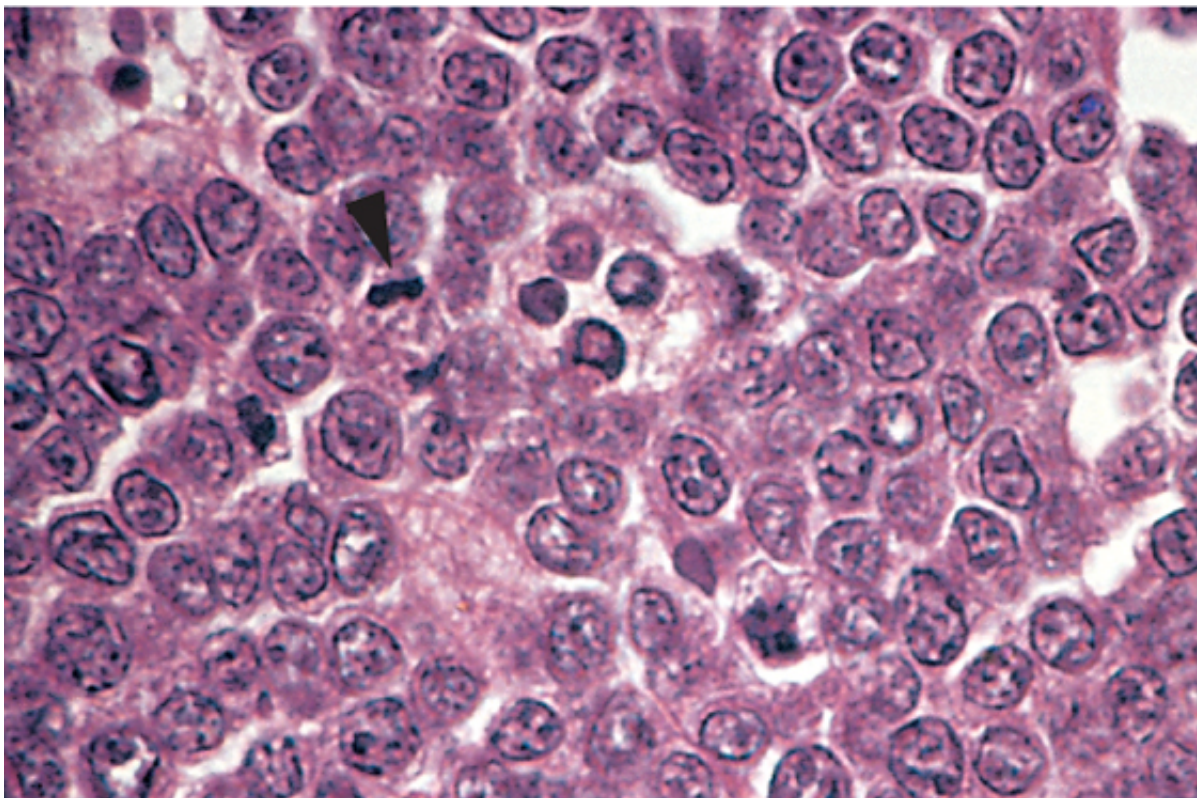
Diffuse large cell B-cell lymphomas are *aggressive tumors that are rapidly fatal if untreated*. With intensive therapy, however, complete remission can be achieved in 60% to 80% of the patients; of these, approximately 30% to 40% survive several years and are often cured. For those not cured with conventional therapy, other more aggressive therapies (e.g., high-dose chemotherapy and bone marrow transplantation) offer some hope. Microarray-based molecular profiling may be used to predict the response to current therapies and perhaps even identify targets for new therapeutic agents.

### **Burkitt Lymphoma**

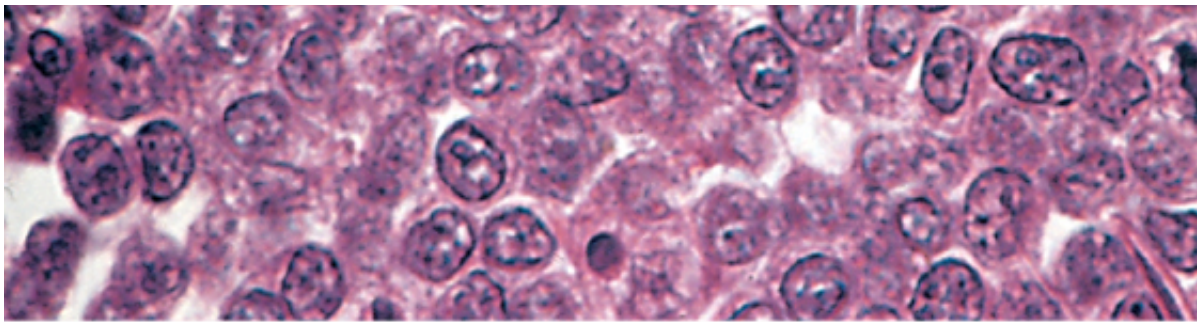
Burkitt lymphoma is endemic in some parts of Africa and sporadic in other areas, including the United States. The endemic and nonendemic diseases are identical, although there are clinical and virologic differences. The relationship to EBV is discussed in [Chapter 6](#).

#### **Morphology**

The tumor cells are uniform and intermediate in size and have round or oval nuclei with **prominent nucleoli** (Fig. 12-18). The nuclear size approximates that of benign macrophages. There is a moderate amount of basophilic or amphophilic cytoplasm, which may contain small, lipid-filled vacuoles. A **high mitotic rate** is very characteristic of this tumor. The presence of numerous tissue macrophages containing ingested tumor cells, accounting for the presence of numerous tissue macrophages containing ingested tumor cells, these benign macrophages are often surrounded by a clear space, they create a "starry sky" appearance.







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Figure 12-18 Burkitt lymphoma. The tumor cells and their nuclei are fairly uniform, giving a monotonous appearance with prominent nucleoli. The "starry sky" pattern produced by interspersed, lightly staining, normal macrophages is better appreciated at lower magnification. (Reprinted with permission of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center.)

### *Immunophenotype and Molecular Features*

These B-cell tumors express surface IgM,  $\kappa$  or  $\lambda$  light chain, the pan-B-cell markers CD19 and CD20. The *IGH* gene is somatically hypermutated, consistent with an origin from a follicular center B cell.

### *Karyotype*

Burkitt lymphoma is always associated with translocations involving the *MYC* gene on chromosome 8 and the *IGH* gene on chromosome 14, but variant translocations involving the  $\kappa$  or  $\lambda$  light chain loci on chromosomes 2 and 22 are also observed. The net result of each is the dysregulation and overexpression of the *MYC* protein, which is discussed in [Chapter 6](#).

### *Clinical Features*

Both the endemic and nonendemic forms affect mainly children and young adults. Burkitt lymphoma is the most common childhood NHL in the United States. In both forms, the disease usually arises at extranodal sites. The maxilla or mandible is the common mode of presentation, whereas abdominal tumors involving the ileocecal region are more common in North America. Leukemic presentations are uncommon, especially in the endemic form, and are distinguished from acute lymphoblastic leukemias, which respond to different drug regimens. Burkitt lymphoma is among the fastest growing human neoplasms; however, with very aggressive chemotherapy regimens, it can be cured.

## **Multiple Myeloma and Related Plasma Cell Disorders**

The common feature that is shared among multiple myeloma and the plasma cell dyscrasias is that the malignant B cell differentiates into plasma cells and secretes a single complete or partial immunoglobulin. Because of the large amounts of immunoglobulins, these disorders have also been called monoclonal gammopathies, and are often referred to as an M component. Although the presence of an M component may be indicative of malignancy, monoclonal components are fairly common in otherwise normal elderly persons, a condition called monoclonal gammopathy of undetermined significance. Collectively these disorders account for about 15% of deaths from tumors of white blood cells in middle-aged and elderly persons.

The plasma cell dyscrasias can be divided into six major variants: (1) multiple myeloma, (2) localized (solitary) plasmacytoma, (3) lymphoplasmacytic lymphoma, (4) heavy-chain disease, (5) primary or immunocyte-associated amyloidosis, and (6) monoclonal gammopathy of undetermined significance. In all forms, the immunoglobulin genes are somatically mutated, and the malignant clone arises from a post-follicular center B cell. Each of these disorders will be briefly described, and then the most common forms will be presented.

### *Multiple Myeloma*

Multiple myeloma, by far the most common of the malignant plasma cell dyscrasias, is a clonal proliferation of plasma cells in the bone marrow that is usually associated with *multifocal lytic lesions throughout the skeletal system*. The malignant plasma cells, also called myeloma cells, is supported by the cytokine interleukin 6 (IL-6), which is

macrophages in the bone marrow stroma. As is true of other B-cell malignancies, it has been applied to have chromosomal translocations involving the IgH locus on chromosome 14. The identified fusion genes are growth factor receptor 3, and cyclin D3 genes; late in the course, translocations involving MYC are also surmised by the list of genes involved by chromosomal translocations, dysregulation of D cyclins is multiple myeloma.

The most common M component is IgG (60%), followed by IgA (20% to 25%); only rarely is it IgM. In 20% of cases, the plasma cells produce *only*  $\kappa$  or  $\lambda$  light chains. Because of their low molecular weight, they are excreted in the urine, where they are termed *Bence-Jones proteins*. Even more commonly, malignant immunoglobulin molecules and free light chains and thus produce both serum M components and the excess light chains have untoward effects on renal function and are an important aspect of the disease.

#### *Localized Plasmacytoma*

These are solitary lesions involving the skeleton or the soft tissues. Skeletal plasmacytomas tend to be multiple myeloma, whereas extraosseous lesions occur mainly in the upper respiratory tract (sinuses, nasal cavity). Immunoglobulin proteins are demonstrable in some of these patients. Those with solitary skeletal plasmacytomas and most develop full-blown multiple myeloma over a period of 5 to 10 years. Extraosseous (soft tissue) plasmacytomas are commonly and are often cured by local resection.

#### *Lymphoplasmacytic Lymphoma*

This tumor is composed of a mixed proliferation of B cells that range from small round lymphocyte-like cells. It behaves like an *indolent B-cell lymphoma* and commonly involves multiple lymph nodes, at the time of presentation. It is included in the plasma cell dyscrasias because the tumor produces an M component. If it is multiple myeloma, it consists in most cases of IgM. Often, the large amount of IgM causes the blood to be called *Waldenström macroglobulinemia*, described below. Other symptoms are related to the infiltration of the bone marrow, by tumor cells. The synthesis of immunoglobulin heavy and light chains is balanced; proteinuria is not seen. Unlike myeloma, this disease *does not produce lytic bone lesions*.

#### *Heavy-Chain Disease*

This is not a specific entity but a group of proliferations in which only heavy chains are produced, and the disease shows a predilection for the lymphoid tissues where IgA is normally produced, such as the ileum. It may represent a variant of MALT lymphoma (discussed later). The less common IgG heavy-chain disease, lymphadenopathy and hepatosplenomegaly and histologically resembles lymphoplasmacytic lymphoma.

#### *Primary or Immunocyte-Associated Amyloidosis*

It may be recalled that a monoclonal proliferation of plasma cells that secrete free light chains underlies multiple myeloma (5). The amyloid deposits (of AL type) consist of partially degraded light chains.

#### *Monoclonal Gammopathy of Undetermined Significance*

Monoclonal gammopathy of undetermined significance (MGUS) is the term applied to monoclonal gammopathy in asymptomatic individuals. M proteins are found in the serum of 1% to 3% of asymptomatic healthy individuals, making this the most common plasma cell dyscrasia. Despite the name, it is increasingly apparent that MGUS *should be considered a form of neoplasia*. Patients with MGUS develop a well-defined plasma cell dyscrasia (multiple myeloma, or amyloidosis) at a rate of 1% per year. Moreover, MGUS cells often contain the same M protein as found in full-blown multiple myeloma. Thus, the diagnosis of MGUS should be made with caution, excluding other forms of monoclonal gammopathies, particularly multiple myeloma. In general, patients with MGUS have monoclonal protein in the serum and no Bence-Jones proteinuria.

### **Morphology**

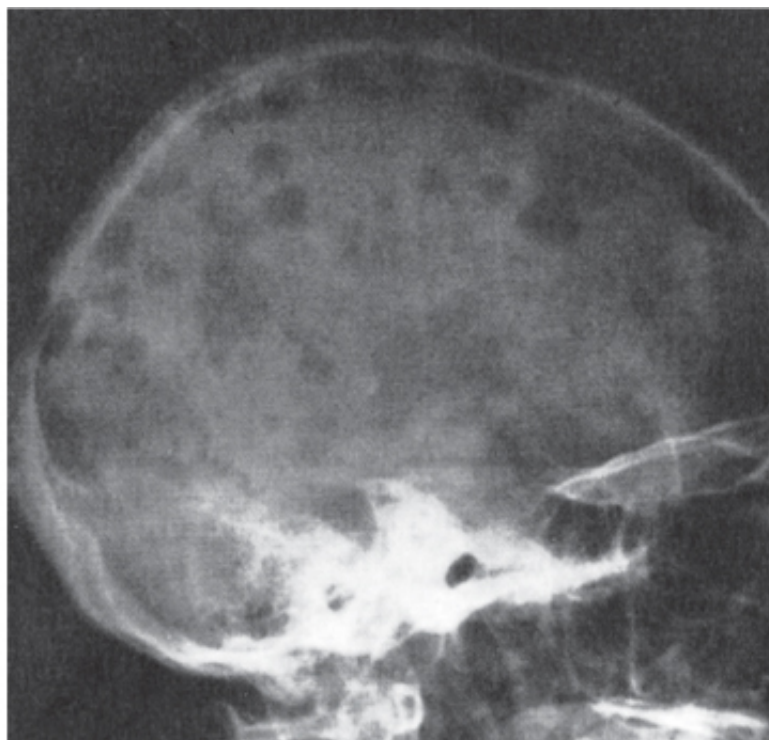
**Multiple myeloma presents most often as multifocal destructive bone lesions.** Although any bone can be affected, the following distribution was found in a series of 100 cases: vertebral column, 66%; ribs, 44%; skull, 41%; pelvis, 28%; femur, 24%; clavicle, 10%. These focal lesions generally begin in the medullary cavity, erode the cancellous bone, and expand the cortex.

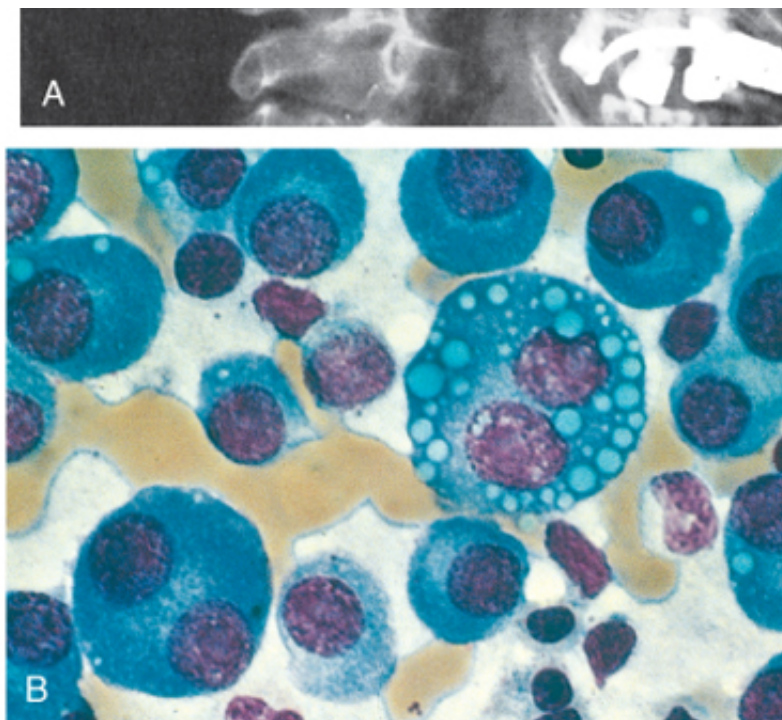
destroy the cortical bone. The bone resorption results from the secretion of certain tumor necrosis factor, IL-6) by myeloma cells. These cytokines stimulate production of RANK-ligand, which promotes the differentiation and activation of osteoclasts. Bone lesions often lead to **pathologic fractures**, which occur most frequently in the vertebral column. Bone lesions usually appear radiographically as **punched-out defects** of 1 to 4 cm in diameter, but in some cases diffuse skeletal demineralization is evident. Microscopic examination reveals an increased number of plasma cells, which constitute 10% to 90% of the marrow cells. Some cells can resemble normal mature plasma cells, but they more often show abnormal features, such as prominent nucleoli or abnormal cytoplasmic inclusions containing immunoglobulin. In advanced, progressive disease, plasma cell infiltrations of soft tissues can be encountered in the lungs, and lymph nodes, or they may be more widely distributed. Terminally, a leuko-

Renal involvement, generally called **myeloma nephrosis**, is a distinctive feature of multiple myeloma. Proteinaceous casts are prominent in the distal convoluted tubules and collecting ducts. These casts are made up of Bence-Jones proteins, but they may also contain complete immunoglobulin, heavy chain protein, and albumin. Some casts have tinctorial properties of amyloid. This is not true amyloid; rather, amyloid is derived from Bence-Jones proteins ([Chapter 5](#)). Multinucleate giant cells and infiltrating macrophages usually surround the casts. **Very often the epithelial cells of the renal tubules become necrotic or atrophic because of the toxic actions of the Bence-Jones proteins.** Metastatic calcification stemming from bone resorption and hypercalcemia may be complicated by systemic amyloidosis, nodular glomerular lesions are present. **Pyelonephritis** occurs as a result of the increased susceptibility to bacterial infections. Less commonly, in advanced disease, abnormal plasma cells are seen.

**In contrast to multiple myeloma, lymphoplasmacytic lymphoma is not associated with bone lesions.** Instead, the neoplastic cells diffusely infiltrate the bone marrow, lymph nodes, and sometimes the liver. Infiltrations of other organs also occur, particularly with disease involving the spleen. The infiltrate consists of lymphocytes, plasma cells, and plasmacytoid lymphocytes of intermediate size. The remaining forms of plasma cell dyscrasias have either already been described (e.g., amyloidosis; [Chapter 5](#)) or are too rare for further description.

#### *Clinical Course*





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 Figure 12-19 Multiple myeloma. **A**, Radiograph of the skull (lateral view). The sharply punched-out bone defects are aspirate. Normal marrow cells are largely replaced by plasma cells, including atypical forms with multiple nuclei containing immunoglobulin.

The clinical manifestations of the plasma cell dyscrasias are varied. They result from the destructive infiltrating neoplastic cells in various tissues and the abnormal immunoglobulins secreted by the tumor. The effects of plasma cell tumors predominate, whereas in lymphoplasmacytic lymphoma most of the effects are due to the effects of the abnormal immunoglobulins in the serum.

The peak age of incidence of multiple myeloma is between 50 and 60 years. The major clinicalopathologic features are summarized as follows:

**Bone pain**, resulting from infiltration by neoplastic plasma cells, is extremely common. Pathologic fractures occur, with focal bone destruction and diffuse resorption. Hypercalcemia can cause neurologic symptoms and lethargy; it also contributes to renal disease. Anemia results from marrow replacement and suppression of hematopoiesis by tumor cells. **Recurrent infections** with bacteria such as *Staphylococcus aureus* and *Escherichia coli* are serious clinical problems. They result from severe suppression of normal immune response. **Hyperviscosity syndrome** may occur due to excessive production and aggregation of immunoglobulins, more characteristic of lymphoplasmacytic lymphoma. **Renal insufficiency** occurs in as many as 50% of patients, due to deposition of immunoglobulin light chain (Bence Jones) proteins on cells lining the tubules. Amyloidosis develops in 5% to 10% of patients.

The diagnosis of multiple myeloma can be strongly suspected when the characteristic focal, punched-out bone lesions are present—especially when located in the vertebrae or calvarium. Electrophoresis of the serum and urine shows that in 99% of cases a monoclonal spike of complete immunoglobulin or immunoglobulin light chain can be demonstrated. In the remaining 1% of cases, monoclonal immunoglobulins can be found within the plasma. Such cases are sometimes called *nonsecretory myelomas*. Examination of the bone marrow is essential for the diagnosis of cell proliferation.

Lymphoplasmacytic lymphoma affects older persons, with the peak incidence being between the ages of 50 and 60 years.



symptoms of this disease can be traced to the presence of large amounts of IgM (macroglobulin), greatly increase blood viscosity. This gives rise to the *hyperviscosity syndrome* known as *Walden* characterized by the following features:

*Visual impairment*, related to the striking tortuosity and distention of retinal veins; retinal hemorrhages contribute to the visual problems  
*Neurologic problems* such as headaches, dizziness, tinnitus  
sluggish blood flow and sludging  
*Bleeding*, related to the formation of complexes between r as interference with platelet functions  
*Cryoglobulinemia*, related to precipitation of macroglobulin  
symptoms such as Raynaud phenomenon and cold urticaria.

Multiple myeloma is a progressive disease, with median survival ranging from 4 to 5 years. The multiple myeloma is somewhat longer, in the range of 4 to 5 years. Although aggressive therapies are being developed, it is presently incurable.

### **Hodgkin Lymphoma**

Hodgkin lymphoma encompasses a distinctive group of neoplasms that arise almost invariably in lymph nodes and spread characteristically in a stepwise fashion to the anatomically contiguous nodes. It is distinguished from other lymphomas for several reasons. First, it is *characterized morphologically by the presence of distinctive Reed-Sternberg (RS) cells*, which are admixed with reactive, nonmalignant inflammatory cells. Second, it has distinctive clinical features, including systemic manifestations such as fever. Third, its histology is stereotypic and different from most other lymphoid neoplasms. Despite these distinguishing features, molecular biology has shown that it is of B-cell origin.

#### **Classification**

Five subtypes of Hodgkin lymphoma are recognized: (1) nodular sclerosis, (2) mixed cellularity, (3) lymphocyte rich, and (4) lymphocyte depletion. The latter two subtypes are uncommon and will not be discussed. In delineating the remaining three, however, we should describe the common denominator among a staging system used to characterize the extent of the disease in an individual.

#### **Morphology**

The sine qua non for Hodgkin lymphoma is the **Reed-Sternberg (RS) cell** (Fig. 12-1) (15-45  $\mu$ m in diameter) with an enlarged multilobated nucleus, exceptionally prominent nucleoli, abundant, usually slightly eosinophilic, cytoplasm. **Particularly characteristic are the large, pale, eosinophilic, inclusion-like acidophilic nuclei or nuclear lobes, each containing a large (inclusion-like) acidophilic nucleolus surrounded by a distinctive clear zone; together they impart an owl-eye appearance. The cell membrane is distinct.** As we will see, such "classic" RS cells are common in the mixed cellularity and lymphocyte-depleted subtypes, uncommon in the nodular sclerosis subtype, and rare in the lymphocyte-predominant subtype. In the latter two subtypes, other characteristic RS cell variants predominate.

The staging of Hodgkin lymphoma (Table 12-9) is of clinical importance, because the extent of disease, the response to therapy, and prognosis are all intimately related to the distribution of the disease.

With this background we can turn to the morphologic classification of Hodgkin lymphoma and point out some of the salient clinical features of each. Later the manifestations of the disease will be presented. The essential features that serve to differentiate the major subgroups (1) nodular sclerosis, and mixed cellularity) are the morphology, immunophenotype, and the nature of the tissue response.

**Nodular Sclerosis Hodgkin Lymphoma.** This is the most common form. It is equally common in men and women and has a striking propensity to involve the lower cervical, supraclavicular, and axillary lymph nodes. Most of the patients are adolescents or young adults, and the overall prognosis is good. It is characterized morphologically by:

The presence of a particular variant of the RS cell, the **lacunar cell** (Fig. 12-2), which has a single multilobate nucleus with multiple small nucleoli and an abundant

has a single multilobate nucleus with multiple small nucleoli and an abundant cytoplasm. In formalin-fixed tissue, the cytoplasm often retracts, giving rise to cells lying in empty spaces, or lacunae. The presence of collagen bands that divide the tissue into circumscribed nodules (Fig. 12-22). The fibrosis may be scant or abundant, may show varying proportions of lymphocytes, eosinophils, histiocytes, and plasma cells, and cells are infrequent.

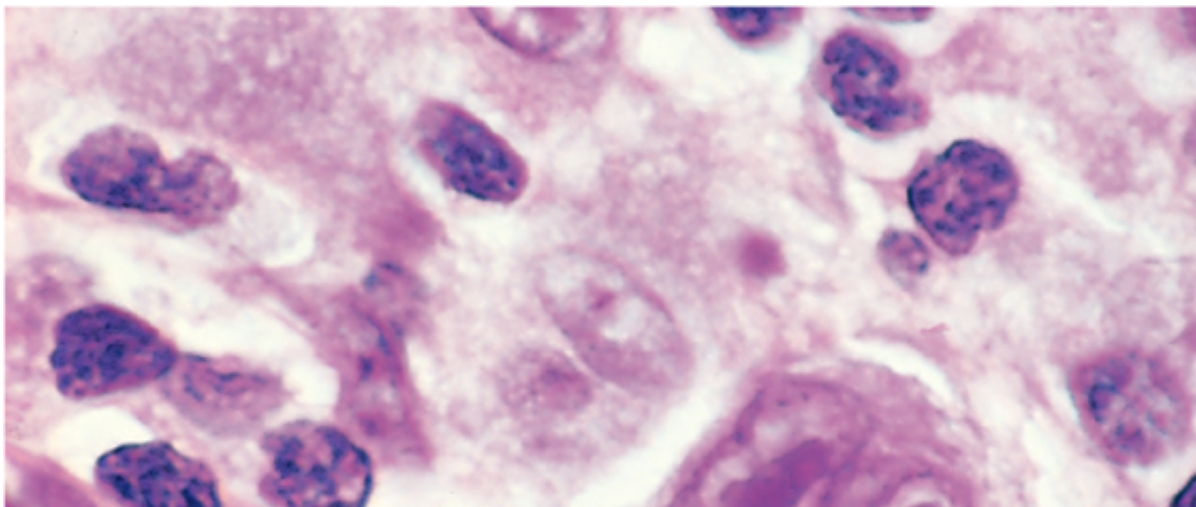
The immunophenotype of the lacunar variants is identical to that of classic RS cells. CD15 and CD30 and usually do not express B- and T-cell-specific antigens.

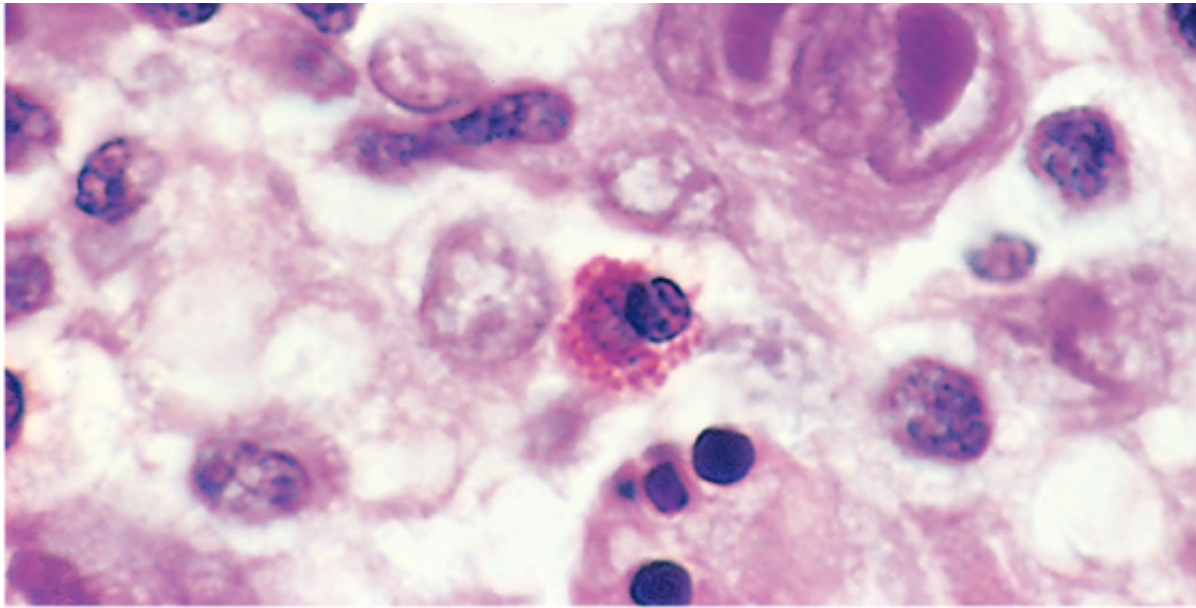
**Mixed-Cellularity Hodgkin Lymphoma.** This is the most common form of Hodgkin lymphoma older than the age of 50 and overall comprises about 25% of cases. There is a mixture of RS cells and other cells. RS cells are plentiful within a distinctive heterogeneous cellular infiltrate, which includes eosinophils, plasma cells, and benign histiocytes (Fig. 12-23). Compared with the classic form, more patients with mixed cellularity have disseminated disease and systemic manifestations.

**Lymphocyte-Predominance Hodgkin Lymphoma.** This subgroup, comprising about 5% of cases, is characterized by a large number of small resting lymphocytes admixed with a few RS cells and benign histiocytes (Fig. 12-24), often within large, poorly defined nodules. Other cells such as eosinophils, neutrophils, and plasma cells, are scanty or absent, and classic Reed-Sternberg cells are difficult to find. Scattered among the reactive cells are lymphohistiocytic (L&H) variants with a delicate multilobed, puffy nucleus that has been likened in appearance to popcorn. The typical nodular growth pattern of lymphocyte-predominance Hodgkin lymphoma has led to the suggestion that it might be a neoplasm of follicular B cells; indeed, phenotypic studies have revealed that L&H variants express B-cell markers (e.g., CD20). Furthermore, L&H variants have rearranged and hypermutated IgH genes, which strongly supports a follicular B-cell origin. Most patients with the disease present with isolated cervical or axillary lymphadenopathy and have a good prognosis.

It is apparent that Hodgkin lymphoma spans a wide range of histologic patterns and that the characteristic fibrosis, eosinophils, neutrophils, and plasma cells, come deceive the pathologist into thinking of an inflammatory reactive process. **The histologic diagnosis of Hodgkin lymphoma requires the definitive identification of RS cells or their variants in the appropriate background of reactive cells.** Immunophenotyping plays an important adjunct role in helping to distinguish Hodgkin lymphoma from reactive conditions and other forms of lymphoma.

In all forms, involvement of the spleen, liver, bone marrow, and other organs may occur. These sites may take the form of irregular nodules that are composed of a mixture of RS cells and reactive cells, or they may be observed in lymph nodes. In advanced disease, the spleen and the liver can be enlarged.



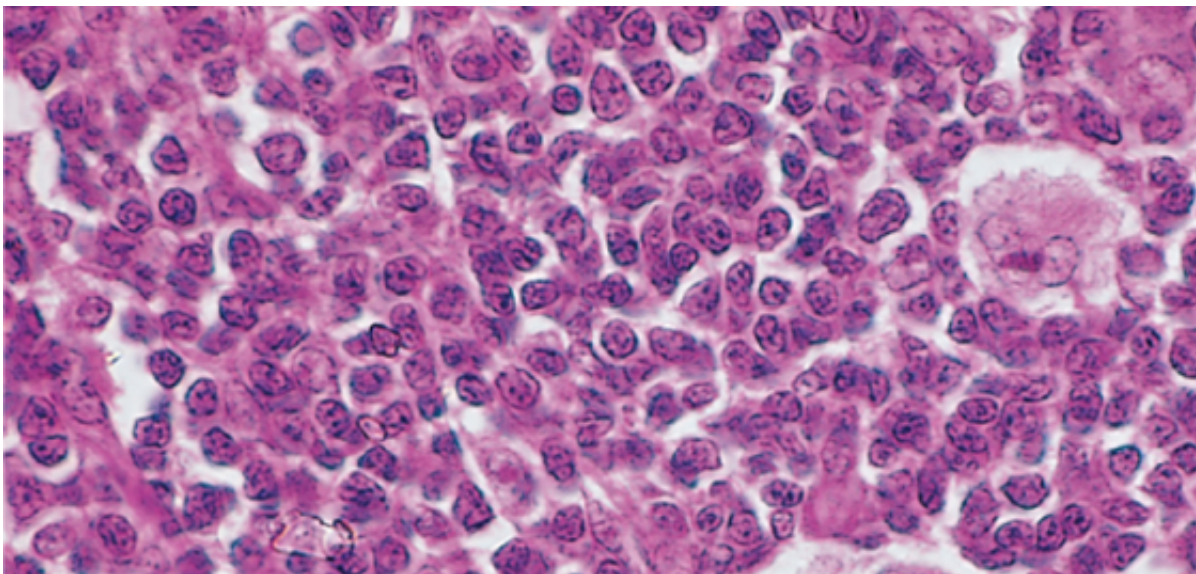


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 Figure 12-20 Hodgkin lymphoma. A binucleate Reed-Sternberg cell with large, inclusion-like nucleoli and abundant eosinophil can be seen below. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texa

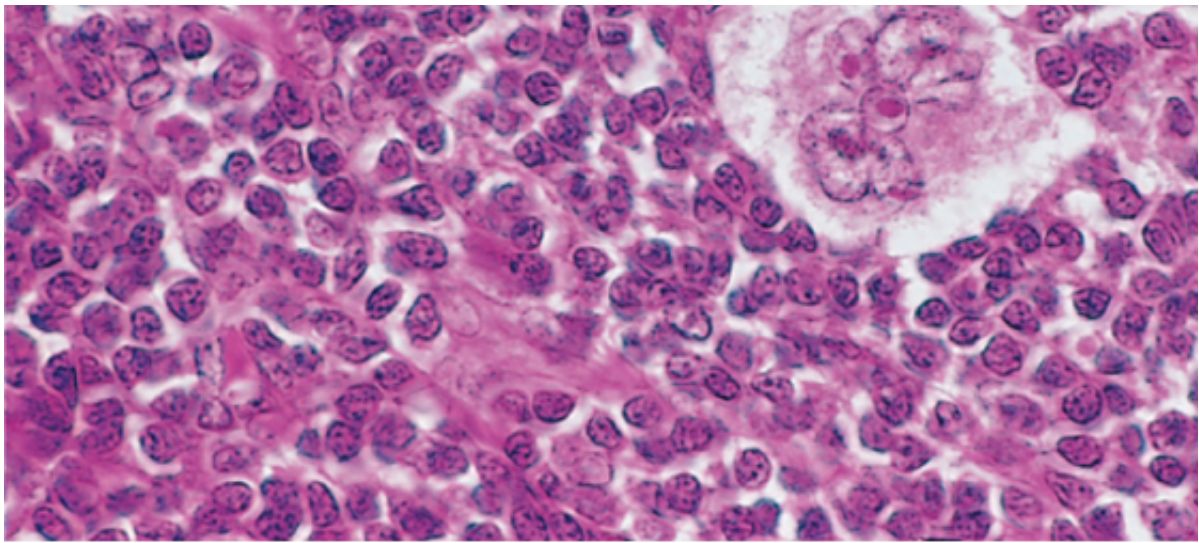
**Table 12-9. Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Cl**  
**Stage Distribution of Disease**

I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tis
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or wi extralymphatic organs or tissue (II <sub>E</sub> )
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spl extralymphatic organ or site (III <sub>E</sub> ), or both (III <sub>ES</sub> )
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with c

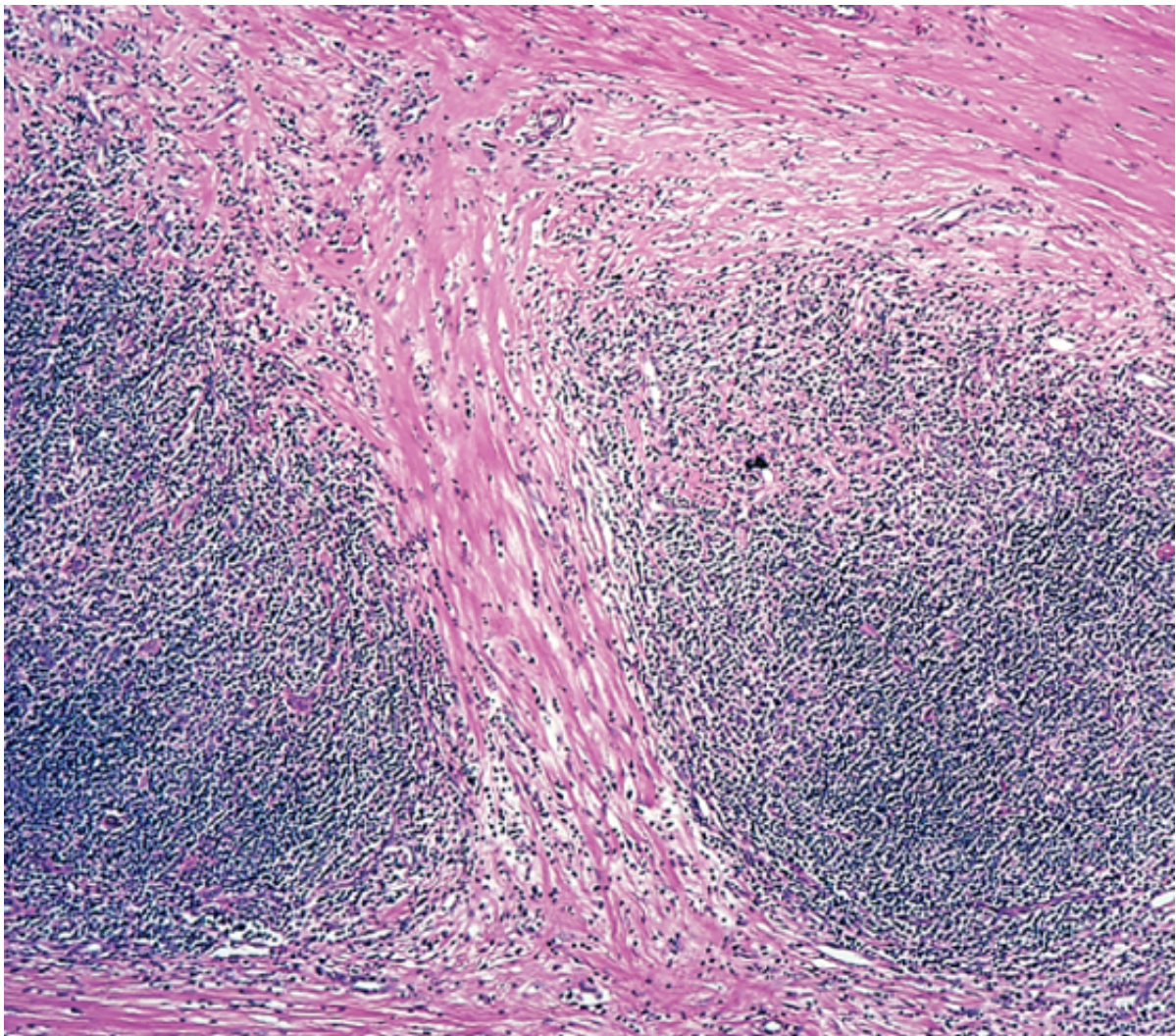
\*All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever  
 10% of normal body weight.  
 From Carbone PT, et al.: Symposium (Ann Arbor): staging in Hodgkin disease. Cancer Res 31:1707, 1971.







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 Figure 12-21 Hodgkin lymphoma, nodular sclerosis type. A distinctive "lacunar cell" with multilobed nucleus contains a clear space created by retraction of its cytoplasm. It is surrounded by lymphocytes. (Courtesy of Dr. Robert W. Miller, University of Texas Southwestern Medical School, Dallas, Texas.)

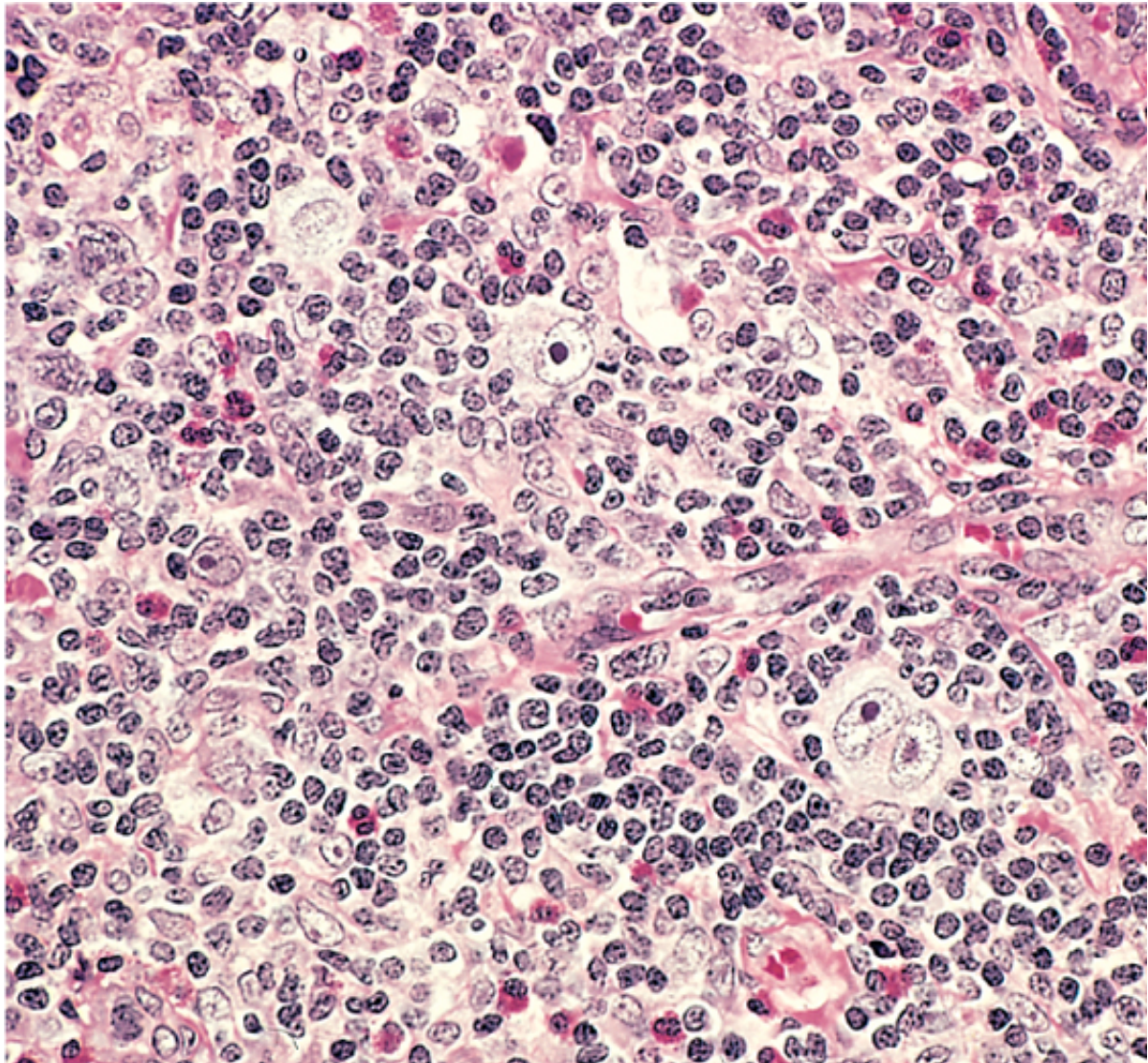






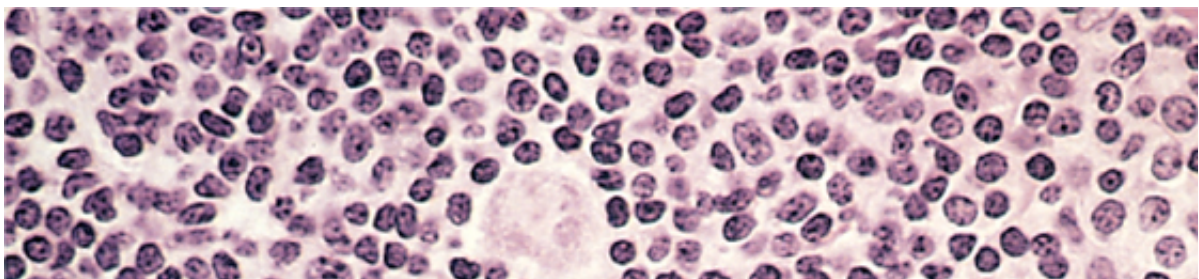
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Figure 12-22 Hodgkin lymphoma, nodular sclerosis type. A low-power view shows well-defined bands of pink, acellular material (sclerotic bands) separating nodules of lymphoid tissue. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas.)

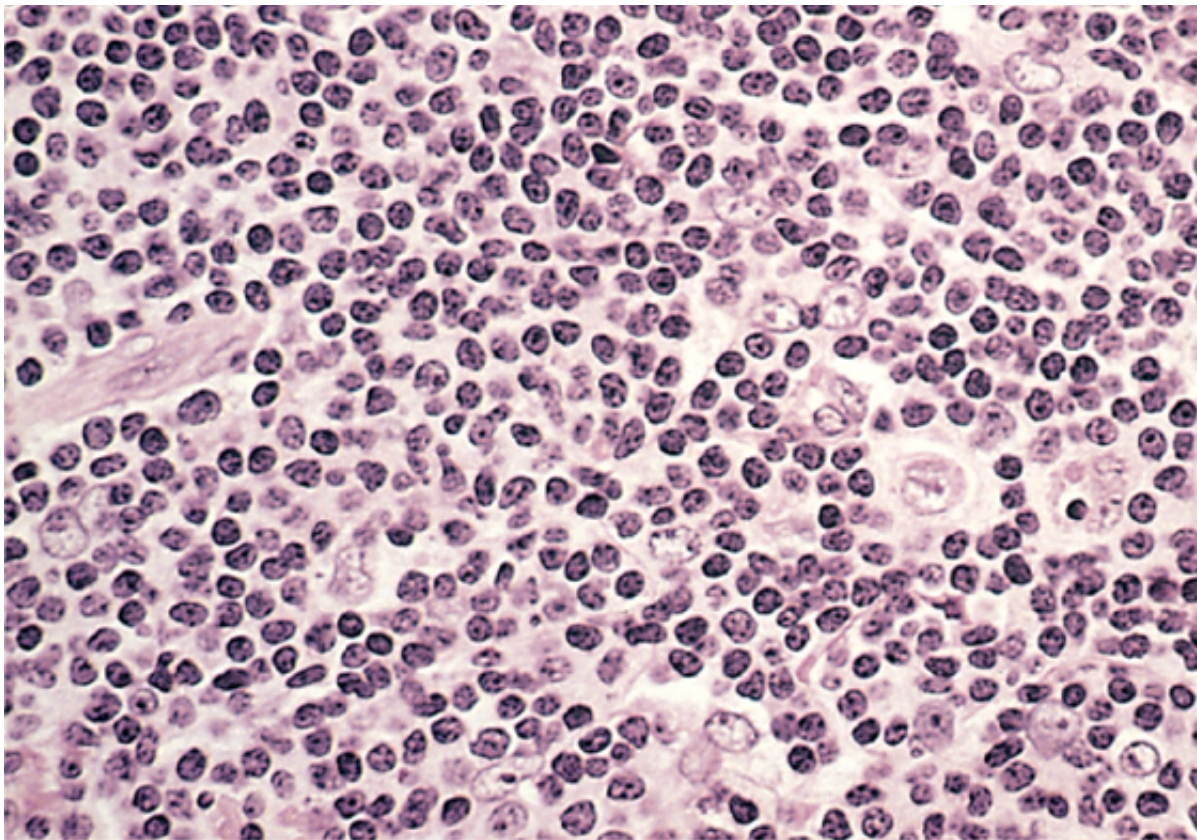


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Figure 12-23 Hodgkin disease, mixed-cellularity type. A diagnostic, binucleate Reed-Sternberg cell is surrounded by a dense infiltrate of lymphocytes (small, dark nuclei) and histiocytes (larger, pale cells with red cytoplasm). (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas.)







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 Figure 12-24 Hodgkin disease, lymphocyte-predominance type. Numerous mature-looking lymphocytes surround histiocytic variants ("popcorn" cells). (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas.)

### *Etiology and Pathogenesis*

Determining the origin of the neoplastic RS cells of Hodgkin lymphoma has proved daunting, in part because of the admixture of these cells with the surrounding reactive inflammatory infiltrate. It has been recognized for some time that the nodular lymphocyte-predominance Hodgkin lymphoma express B-cell markers, supporting a B-cell origin. The origin of the other forms of Hodgkin lymphoma have been enigmatic, in that they generally do not express lineage-specific markers. This question was finally resolved by elegant studies performed on single microdissected RS cells obtained from patients with nodular sclerosing Hodgkin lymphoma. Sequence analysis of DNA amplified from such cells has shown that the RS cell possesses the same immunoglobulin gene rearrangements as its neighbor and that the rearrangement has undergone somatic hypermutation. As a result, it is now agreed that *Hodgkin lymphoma is a neoplasm*

This said, many puzzles remain to be answered. RS cells are aneuploid but lack the chromosomal abnormalities characteristic of germinal center B-cell lymphomas and have patterns of gene expression that bear little resemblance to those of normal B cells. How do these cells transform and alter their appearance and gene expression programs are still unknown. The role of EBV. The EBV genome is present in the RS cells in as many as 70% of cases of the mixed-cellularity type and in all cases of the nodular sclerosing type. More importantly, the integration of the EBV genome is identical in all RS cells, suggesting that EBV infection precedes (and therefore may be related to) transformation. Thus, as in Burkitt lymphoma and in immunodeficient patients, EBV infection is likely to be one of several steps contributing to the development of Hodgkin lymphoma, particularly the mixed-cellularity type.

If EBV is playing a causative role, are there common oncogenic signals in EBV-positive and EBV-negative Hodgkin lymphoma? From the observation that the RS cells in classical forms of Hodgkin lymphoma, regardless of their EBV status, express activated NF- $\kappa$ B, a transcription factor that normally stimulates B-cell proliferation and protects B cells from apoptosis, it is clear that EBV proteins that are known to activate NF- $\kappa$ B are expressed in EBV-positive RS cells. Somatic mutations in the NF- $\kappa$ B pathway are also found in EBV-negative RS cells.

EBV proteins that are known to activate NF- $\kappa$ B are expressed in EBV-positive RS cells. Conversely, I $\kappa$ B, an important inhibitor of NF- $\kappa$ B, have been found in EBV-negative RS cells. Thus, hyperactivation promotes proliferation, genesis, growth, and survival of RS cells.

The characteristic non-neoplastic, inflammatory-cell infiltrate seems to result from a number of cytokines (which attracts and activates eosinophils), transforming growth factor  $\beta$  (a fibrogenic factor), and interleukin-6 (through an autocrine mechanism). Conversely, the responding inflammatory cells, rather than being inhibitory (such as CD30 ligand) that can aid the growth and survival of RS cells, and contribute further to the disease.

### Clinical Course

**Table 12-10. Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas**

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)	More frequent in advanced stages
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring often involved
Extranodal involvement uncommon	Extranodal involvement common

Hodgkin lymphomas, like NHLs, usually present as a painless enlargement of the lymph nodes. A definitive diagnosis can be made only by examination of a lymph node biopsy specimen, several clinical features favor Hodgkin lymphoma (Table 12-10). Younger patients with the more favorable histologic types tend to present in clinical stages I and II. Systemic manifestations are uncommon. Patients with disseminated disease (stages III and IV) are more likely to have B symptoms (fever, night sweats, and weight loss). As mentioned earlier, these patients generally have a good prognosis. The outlook after aggressive radiotherapy and chemotherapy for patients with this disease is generally very good. *With current modalities of therapy, the clinical stage is the most important prognostic factor.* The survival rate of patients with stage I-A or II-A disease is close to 100%. Even with advanced disease, the disease-free survival rate is around 50%. However, therapeutic successes have also brought problems. Radiotherapy protocols are at much higher risk of developing certain malignancies, including lung cancer. As a result, current efforts are aimed at developing less genotoxic therapeutic regimens that decrease toxicity while preserving a high cure rate.

### Miscellaneous Lymphoid Neoplasms

Of the many remaining forms of lymphoid neoplasia within the WHO classification, several with diagnostic and therapeutic interest merit brief discussion.

#### Extranodal Marginal Zone Lymphoma

This is a special category of low-grade mature B-cell tumors that arise most commonly in mucosa-associated lymphoid tissue (MALT) such as salivary glands, small and large bowel, and lungs, and some nonmucosal sites such as the thyroid. These lymphomas tend to develop in the setting of autoimmune disorders (such as Sjögren syndrome) or chronic infections with such organisms as *Helicobacter pylori* and *Campylobacter jejuni*, suggesting that these organisms contribute to lymphomagenesis. In the case of *H. pylori*-associated gastric MALT lymphoma, eradication of the bacteria often leads to regression of the tumor cells, which seem to depend on cytokines secreted by the bacteria for growth and survival (Chapter 6). When arising at other sites, MALT tumors can often be cured by local therapy. Recurrent cytogenetic abnormalities are recognized: t(1;14), involving the *BCL10* and *IgH* genes; and t(12;22), involving the *IAP2* genes.

#### Hairy Cell Leukemia

This uncommon, indolent B-cell neoplasm is distinguished by the presence of leukemic cells that have characteristic "hairy" projections. The tumor cells express pan-B-cell markers, including CD19 and CD20, surface immunoglobulin, and CD11c and CD103; these two antigens are not present on most other B-cell tumors, making them

This tumor occurs mainly in older males, and its *manifestations result largely from infiltration of bone marrow and spleen*, which is often massive, is the most common and sometimes the only abnormal physical finding. *F* bone marrow infiltration and splenic sequestration is seen in more than half the cases. Hematomegaly is less common.

infiltration and splenic sequestration, is seen in more than half the cases. Hepatomegaly is less common. Lymphadenopathy is distinctly rare. *Leukocytosis is not a common feature*, being present in only 10% of cases. The disease is indolent but progressive. The major problems are bleeding and infection. Unlike most other low-grade lymphoid neoplasms, this tumor is extremely sensitive to purine nucleosides. Complete durable responses are the rule, and the overall prognosis is good.

### *Mycosis Fungoides and Sézary Syndrome*

These are composed of neoplastic CD4+ T cells that home to the skin; as a result, they are often called *lymphomas*.

Mycosis fungoides usually presents as a nonspecific erythrodermic rash, which over time tends to progress to tumor phase. Histologically, there is infiltration of the epidermis and upper dermis by neoplastic T cells. The nuclei are characterized by marked infolding of the nuclear membrane. With progressive disease, blastic cells may appear. Sézary syndrome is a clinical variant characterized by the presence of (1) a generalized erythroderma and (2) Sézary cells in the peripheral blood. Circulating tumor cells are also present in as many as 50% of patients with mycosis fungoides. Patients with erythrodermic-phase mycosis fungoides often survive for many years, whereas the prognosis is poor for patients with tumor-phase disease, visceral disease, or Sézary syndrome.

### *Adult T-Cell Leukemia/Lymphoma*

This T-cell neoplasm is caused by a retrovirus, human T-cell leukemia virus type 1 (HTLV-1). It is endemic in the Caribbean basin, and West Africa and occurs sporadically elsewhere, including in the southeastern United States. The tumor is discussed in [Chapter 6](#). In addition to causing lymphoid malignancies, HTLV-1 infection can cause a progressive demyelinating disease that affects the central nervous system and the spinal cord.

Adult T-cell leukemia/lymphoma is characterized by skin lesions, generalized lymphadenopathy, and variable numbers of malignant CD4+ lymphocytes in the peripheral blood. The leukemic cells express the T-cell receptor  $\alpha$  chain. In most cases this is an extremely aggressive disease, with a median survival time of less than 2 years. In some patients the course of the disease is chronic; their disease is clinically indistinguishable from cutaneous T-cell lymphoma.

### *Peripheral T-Cell Lymphomas*

This is a heterogeneous group of tumors that together make up about 15% of adult NHLs. Although they are grouped under this heading, most tumors in this group are unclassifiable. In general, they present as disseminated disease and respond poorly to therapy.

## **SUMMARY**

### **Lymphoid Neoplasms**

*Classified based on cell of origin and stage of differentiation* Most common types are *B-cell lymphoblastic leukemias and lymphomas*, which are derived from B- and T-lymphocytes.

Highly aggressive tumors that present with symptoms of bone marrow failure. Tumor cells contain genetic lesions that block differentiation and accumulation of immature blasts that cannot function as immune cells.

*Most common types in adults are non-Hodgkin lymphomas derived from germinal center B cells.*

May be indolent (e.g., follicular lymphoma) or aggressive (e.g., diffuse large B-cell lymphoma). Sometimes interfere with the immune system by dysregulating normal B and T cells (e.g., chronic lymphocytic leukemia, multiple myeloma). Often associated with chromosomal translocations or mutations involving genes (such as *BCL-2*) that regulate normal mature B-cell development and survival.

*Precursor B- and T-Cell Lymphoblastic Leukemia/Lymphoma:*

Aggressive tumors of pre-B or pre-T cells that are most common in children and young adults, but which occur throughout life. Most patients present with bone marrow failure by extensive marrow replacement by leukemic cells, resulting in pancytopenia.

*Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia:*

Tumor of mature B cells that usually presents with involvement of the lymph nodes. Follows an indolent course, commonly associated with



lymph nodes. Follows an indolent course, commonly associated with immunodeficiency, including an increased susceptibility to infection and auto-immune disease.

**Follicular Lymphoma:**

Tumor cells recapitulate the growth pattern of normal germinal centers. Some cases are associated with a t(14;18) translocation that results in the over-expression of the anti-apoptotic protein BCL2.

**Mantle Cell Lymphoma:**

Tumor of mature B cells that usually presents with advanced disease involving the bone marrow, and extranodal sites such as the gut. Highly associated with a t(12;21) translocation that results in over-expression of cyclin D1, a regulator of cell growth.

**Diffuse Large B-Cell Lymphoma:**

Heterogeneous group of mature B cell tumors that share a similar but aggressive clinical behavior; the most common type of lymphoma. High frequency of chromosomal rearrangements or mutations of the *BCL6* gene; one-third arise from follicular lymphoma and carry a t(14;18) translocation.

**Burkitt Lymphoma:**

Very aggressive tumor of mature B cells that usually arises at extranodal sites. Associated with translocations involving the *c-MYC* proto-oncogene, and with latent infection by Epstein-Barr virus (EBV).

**Multiple Myeloma:**

Plasma cell tumor that usually presents as multiple lytic bone lesions and hypercalcemia. Neoplastic plasma cells may suppress normal hematopoiesis and secrete partial immunoglobulins that are often nephrotoxic.

**Hodgkin Lymphoma:**

Unusual tumor mostly comprised of reactive lymphocytes, macrophages, and a malignant cell, the Reed-Sternberg cell (which is derived from B cells). The Reed-Sternberg cell is a minor fraction of the tumor mass.

See also Table 2-8 for features of different tumors.

## Myeloid Neoplasms

*Myeloid neoplasms arise from hematopoietic stem cells and typically give rise to monoclonal proliferation of myeloid cells.* There are three general categories of myeloid neoplasia. In the AMLs, the neoplastic clone interferes with normal myeloid cell development. Immature myeloid cells (blasts), which can exhibit evidence of granulocytic, erythroid, or megakaryocytic differentiation, accumulate in the marrow, replacing normal elements, and frequently cause cytopenias. In the *chronic myeloproliferative disorders*, the neoplastic clone retains the capacity to undergo terminal differentiation and regulated growth. Commonly there is an increase in one or more of the formed elements (red cells, white cells, or platelets) in the peripheral blood. In the *myelodysplastic syndromes*, terminal differentiation occurs but in a dysregulated manner, leading to the appearance of dysplastic marrow precursors and peripheral blood cytopenias.

Although these three categories provide a useful starting point when considering the myeloid neoplasms, the lines between them are sometimes blurred. Both myelodysplastic syndromes and myeloproliferative disorders often transform into acute myelogenous leukemia, and some patients present with disorders that have features of both myeloid neoplasms. Given that all arise from hematopoietic stem cells, the close relationship among these categories is evident.

## Acute Myelogenous Leukemia

AML primarily affects older adults, with the median age being 50 years. It is an extremely heterogeneous disease. The clinical signs and symptoms, which closely resemble those produced by ALL, are usually nonspecific and include fatigue, pallor, abnormal bleeding, and fever. The replacement of normal marrow elements by leukemic blasts. Fatigue and pallor, abnormal bleeding, and fever are common in newly diagnosed patients, who typically present within a few weeks of the onset of symptoms. Splenomegaly is usually present but is generally less prominent than in ALL, but, rarely, AML presents as a discrete tissue mass (a so-called testicular AML). The diagnosis and classification of AML are based on the results of morphologic, histochemical, immunophenotypic, and cytogenetic tests. Karyotyping is most predictive of outcome.

*Pathophysiology*

### *Pathophysiology*

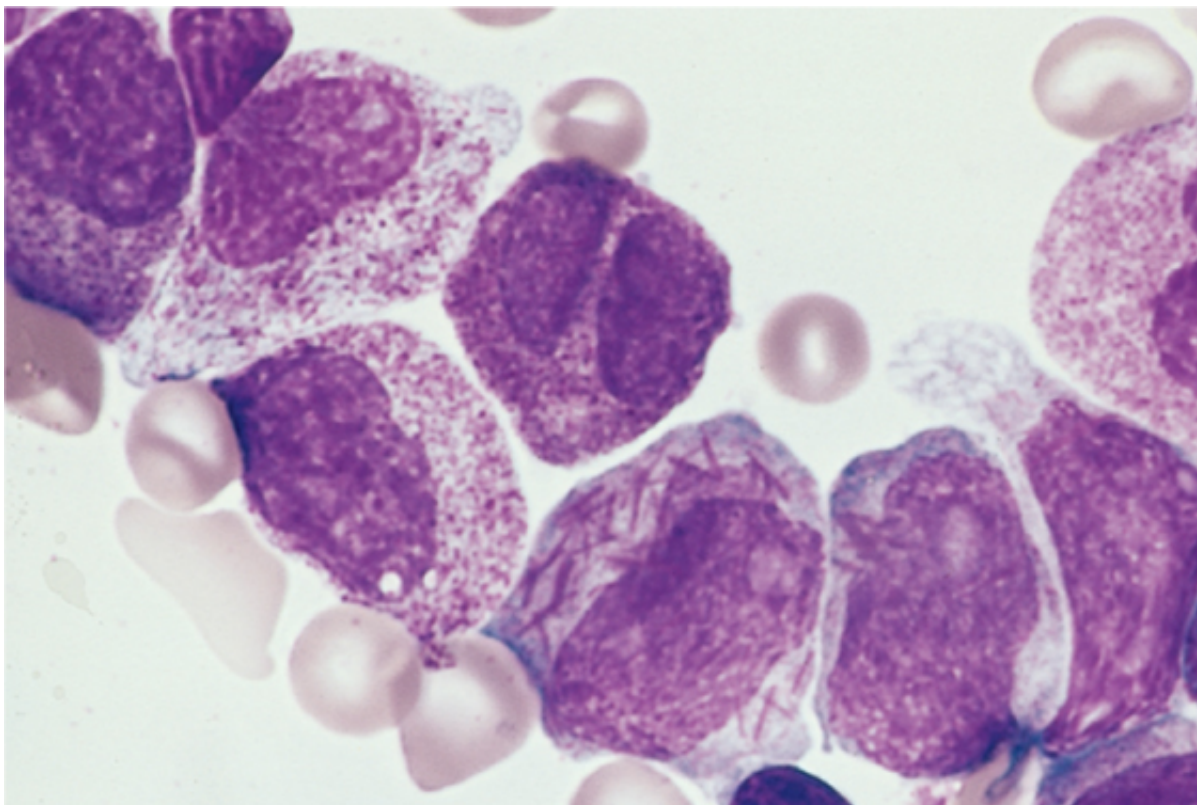
Most AMLs are associated with acquired mutations in transcription factors that inhibit normal myeloid accumulation of cells at earlier stages of development. Of particular interest is the t(15;17) translocation. This translocation results in the fusion of the retinoic acid receptor  $\alpha$  (*RARA*) gene on chromosome 15. The chimeric gene(s) produce abnormal PML/*RARA* fusion proteins that block myeloid differentiation, probably by inhibiting the function of normal *RARA* receptors. Remarkably, pharmacologic doses of all-trans retinoic acid (ATRA), a retinoic acid analogue, overcome this block and cause the neoplastic promyelocytes to terminally differentiate. Neutrophils live, on average, for 6 hours; the result is the rapid clearance of tumor cells and remission. The effect is very specific; AMLs without translocations involving *RARA* do not respond to retinoic acid alone, possibly because the neoplastic progenitor that gives rise to the promyelocytes is resistant to retinoic acid. However, when combined with chemotherapy, the prognosis is excellent. Nonetheless, ATRA is an effective therapy that is targeted at a tumor-specific molecular defect.

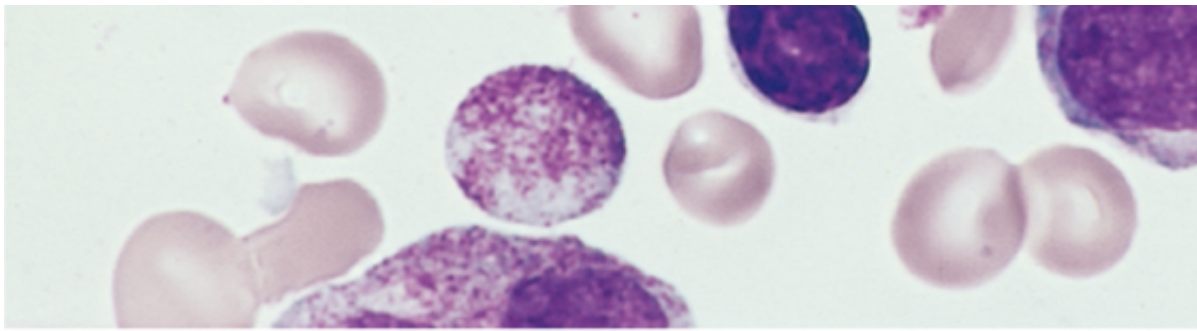
Other work using transgenic or gene knock-in mice has generally suggested that the mutated transcription factor is sufficient, in and of itself, to cause the disease. Complementary mutations have been described that have no effect on maturation but instead promote enhanced proliferation and survival. One example is gain of function of the *FMS* (a surface receptor with tyrosine kinase activity), which are seen in a number of AML subtypes, including

### **Morphology**

By definition, in AML myeloid blasts or promyelocytes make up more than 20% of the cellular population. **Myeloblasts** (precursors of granulocytes) have delicate nuclear chromatin and fine, azurophilic granules in the cytoplasm (see Fig. 12-14B). Distinctive red-staining granules (**Auer rods**) may be present in myeloblasts or more differentiated cells; they are pathognomonic of myeloblasts and are thus a helpful diagnostic clue when present. In other subtypes, promyelocytes, monoblasts, or megakaryoblasts predominate.

### *Classification*





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Figure 12-25 Acute promyelocytic leukemia (M3 subtype). Bone marrow aspirate shows neoplastic promyelocytes with granules. Other characteristic findings include the presence of several cells with bilobed nuclei and a cell in the center with Auer rods. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center)

AMLs are diverse in terms of genetics, the predominant line of differentiation, and the maturity of the cells. This diversity is the basis for the Revised French-American-British (FAB) classification (Table 12-11A), which is still used. However, it has been shown that the FAB classification has limited prognostic value, whereas *certain recurrent chromosomal abnormalities and a history of a myelodysplastic syndrome are predictive of outcome*. As a result, a new WHO classification has been proposed that takes these variables into account (Table 12-11B). The FAB categories are used within the WHO classification as prognostic factors.

#### Histochemistry

Cases with granulocytic differentiation are typically positive for the enzyme myeloperoxidase, which reacts with peroxidase substrates. Auer rods are intensely peroxidase positive, which can help bring out their characteristic appearance. Differentiation is demonstrated by staining for lysosomal nonspecific esterases.

#### Immunophenotype

The expression of immunologic markers is heterogeneous in AML. Most express some combination of CD13, CD14, CD15, CD64, or CD117 (cKIT). CD33 is expressed on pluripotent stem cells but not on more differentiated cells. Such markers are helpful in distinguishing AML from ALL (as shown in Fig. 12-14) and identifying subtypes. In addition, monoclonal antibodies reactive with platelet-associated antigens are very helpful in the diagnosis of acute megakaryocytic leukemia.

#### Prognosis

AML is a devastating disease. Tumors with "good-risk" karyotypic aberrations (t[8;21], inv[16]) are associated with improved short-term disease-free survival, but the overall long-term disease-free survival is only 15% to 30% with current therapy. As the number of patients with AML are being treated with more aggressive approaches, such as allogeneic bone marrow transplantation.

#### Myelodysplastic Syndromes

In patients with these disorders, the bone marrow is partly or wholly replaced by the clonal progenitor that retains the capacity to differentiate into red cells, granulocytes, and platelets, but in a manner that is abnormal. As a result the bone marrow is usually hypercellular or normocellular, but the peripheral blood shows abnormalities. The abnormal stem cell clone in the bone marrow is genetically unstable, which leads to acquisition of additional mutations that lead to transformation to AML. Most cases are idiopathic, but some develop after chemotherapy with alkylating agents or radiation therapy.

Cytogenetic studies reveal that a chromosomally abnormal clone of cells is present in the marrow in this disease. Some common karyotypic abnormalities include loss of chromosomes 5 or 7, or deletion of chromosome 17p. The marrow is populated by abnormal-appearing hematopoietic precursors. Some of the more common abnormalities include erythroid precursors resembling those seen in the megaloblastic anemias, erythroid forms with iron-laden granules (ringed sideroblasts), granulocyte precursors with abnormal granules or nuclear maturation, and blasts with abnormal nuclei.

**Table 12-11A. Revised FAB Classification of Acute Myelogenous Leukemias**

Class Definition		Incidence (% of AML)	Morphology/Comments
M0	Minimally differentiated AML	2-3	Blasts lack Auer rods and myeloperoxidase but express myeloid lineage markers
M1	AML without maturation	20	Some blasts (≥3%) are myeloperoxidase positive; few granules or Auer rods beyond the myeloblast stage of differentiation.
M2	AML with maturation	30-40	>20% of marrow cells are myeloblasts, but many cells are seen at later stages of maturation; Auer rods are usually present; often associated with t(8;21).
M3	Acute promyelocytic leukemia	5-10	Most cells are abnormal promyelocytes, often containing many Auer rods; average (median age 35-40yr); high incidence of DIC; strongly associated with t(15;17)
M4	Acute myelomonocytic leukemia	15-20	Myelocytic and monocytic differentiation evident by cytochemical stains; nonspecific esterase; myeloid cells show a range of maturation; variably associated with inv(16).
M5	Acute monocytic leukemia	10	Monoblasts and immature monocytic cells (myeloperoxidase negative) predominate; Auer rods are usually absent; older patients; more likely to have lymphadenopathy, and tissue infiltration; the M5b subtype is defined by the presence of appearing monocytes in the peripheral blood, whereas only immature monocytes are seen in the marrow in M5a.
M6	Acute erythroleukemia	5	Most commonly associated with abundant dysplastic erythroid progenitors; nonerythroid cells are myeloblasts, which may contain Auer rods; usually associated with exposure to mutagens (e.g., chemotherapy).
M7	Acute megakaryocytic leukemia	1	Blasts of megakaryocytic lineage predominate, as judged by expression of CD41 and CD61; myelofibrosis or increased marrow reticulin often present; Auer rods are usually absent.

DIC, disseminated intravascular coagulation.

**Table 12-11B. Proposed WHO Classification of Acute Myelogenous Leukemia**

Class
<b>I. AML with Recurrent Chromosomal Translocations</b>
AML with t(8;21)(q22;q22); <i>CBFα/ETO</i> fusion gene
AML with inv(16)(p13;q22); <i>CBFβ/MYH11</i> fusion gene
AML with t(15;17)(q22;q21.1); <i>PML/RARα</i>
AML with t(11q23;variant)
<b>II. AML with Multilineage Dysplasia</b>
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome
<b>III. AML, Therapy-Related</b>
Alkylating agent related
Epipodophyllotoxin related
<b>IV. AML, Not Otherwise Classified</b>
Subclasses defined by extent and type of differentiation (M0-M7)

Most individuals with this disease are between 50 and 70 years of age. AML develops in 10% to 40% of patients with aplastic anemia, and hemorrhages, as a result of the defective bone marrow function. The response to chemotherapy support to the idea that myelodysplasia arises in a background of stem cell failure. It is of interest that patients with aplastic anemia eventually develop a myelodysplastic syndrome, and a significant minority of patients with myelodysplastic syndrome eventually develop acute myelogenous leukemia. In this subset of patients, it is possible that the malignant clone "grows" in the absence of attack by T cells. As discussed earlier, a similar mechanism seems to underlie paroxysmal nocturnal hemoglobinuria.



variable; the median survival time varies from 9 to 29 months and is worse in those with increased abnormalities at the time of diagnosis.

### **Chronic Myeloproliferative Disorders**

These disorders are marked by the hyperproliferation of neoplastic myeloid progenitors that retain as a result, there is an increase in one or more formed elements of the peripheral blood. The neoplastic secondary hematopoietic organs (the spleen, liver, and lymph nodes), resulting in hepatosplenomegaly and extramedullary hematopoiesis) and mild lymphadenopathy. A common theme is the association of tyrosine kinases, which generate high-intensity constitutive signals that mimic those that regulate the growth of normal myeloid cells. This insight provides a satisfying explanation for the observed overproduction of myeloid cells and the availability of tyrosine kinase inhibitors.

Most patients with this disease subgroup fall into one of four diagnostic entities: chronic myelogenous leukemia (PCV), primary myelofibrosis, and essential thrombocythemia. CML is clearly separated from the other myeloproliferative disorders by a characteristic abnormality, the presence of a *BCR-ABL* fusion gene. In contrast, the other myeloproliferative disorders overlap clinically and genetically. Mutations of the JAK2 kinase are the single most common gene abnormality in these disorders: >90% of cases of polycythemia vera, 50% of primary myelofibrosis, and 30% of essential thrombocythemia. In addition, many myeloproliferative disorders are associated with activating mutations in still other tyrosine kinases, such as the platelet-derived growth factor receptor alpha and beta. Thus, an evolving theme is that *most, if not all, myeloproliferative disorders are associated with an increase in the activity of one or another tyrosine kinase, which appears to stimulate the same signaling pathway activated by hematopoietic growth factors*. Only CML, PCV, and primary myelofibrosis are present in this subgroup; the other myeloproliferative disorders occur too infrequently to merit discussion.

#### **Chronic Myelogenous Leukemia**

CML principally affects adults between 25 and 60 years of age and accounts for 15% to 20% of all leukemias in the fourth and fifth decades of life.

#### **Pathophysiology**

CML is uniformly associated with the presence of an acquired genetic abnormality, a *BCR-ABL* fusion gene. The *BCR-ABL* fusion gene is the product of a (9;22) translocation that moves the *ABL* gene from chromosome 9 to chromosome 22 adjacent to the *BCR* gene. The derivative chromosome 22 is often referred to as the Philadelphia chromosome, discovered in Philadelphia. In the remaining 5% of patients, the *BCR-ABL* fusion gene is created by a reciprocal translocation between chromosomes 9 and 22, cytogenetically cryptic or obscured by the involvement of more than two chromosomes. In individuals with CML, the *BCR-ABL* fusion gene is present in granulocytic, erythroid, megakaryocytic, and B-cell precursors, and in some cases T-cell precursors, providing evidence for the origin of CML from a pluripotent stem cell. As you recall from Chapter 6, the *BCR-ABL* fusion gene, consisting of portions of *BCR* and the tyrosine kinase domain of *ABL* that is critical for neoplastic transformation, is highly characteristic of CML, it should be remembered that it is also present in 25% of adults with AML.

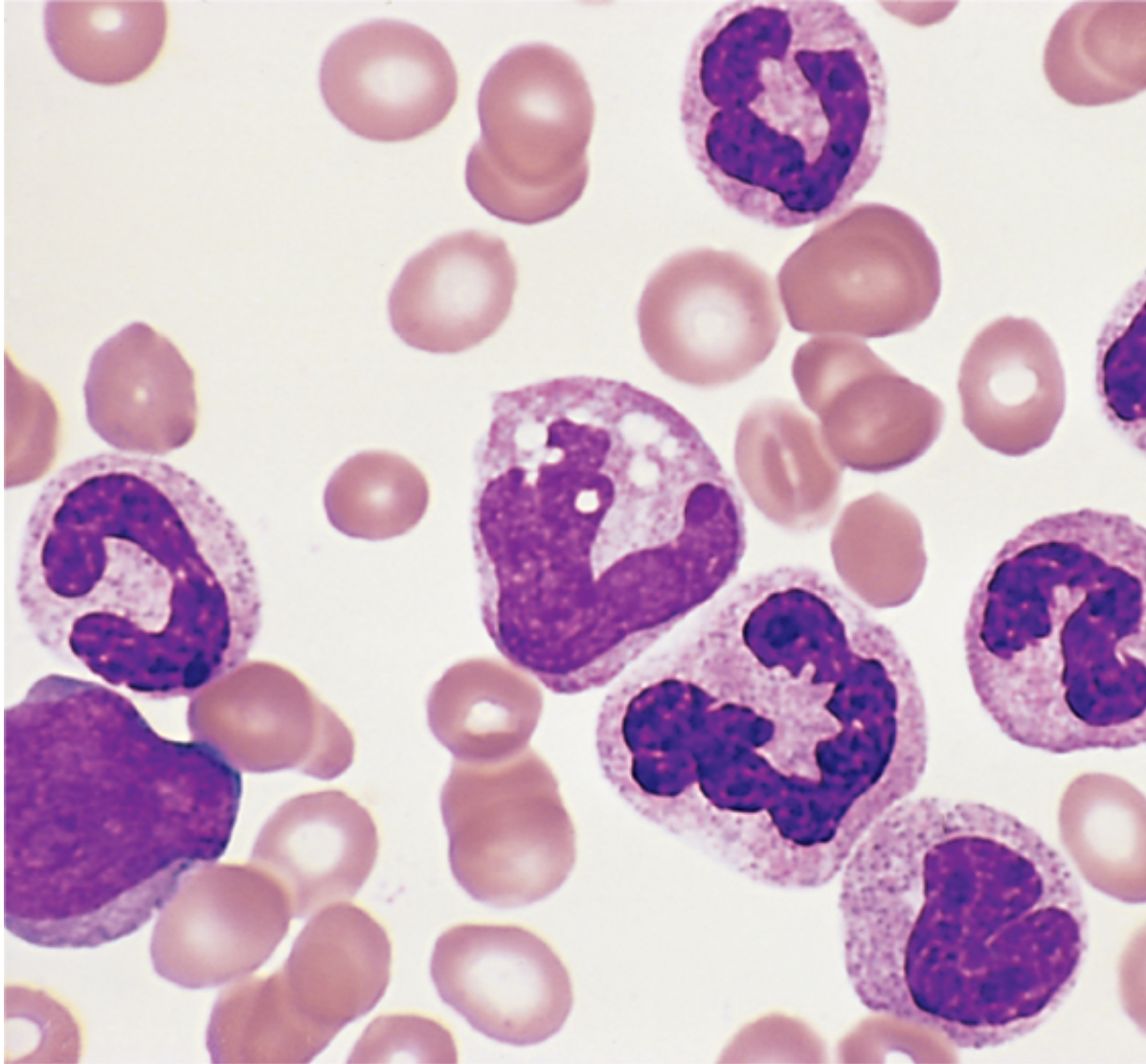
Normal myeloid progenitors depend on signals generated by growth factors and their receptors for growth. In CML, the progenitors have much decreased requirements. This altered growth-factor dependence is due to the constitutive activity of the *BCR-ABL* kinase, which generates constitutive signals that mimic the effects of growth-factor receptor activation. Because the *BCR-ABL* kinase is present in multiple lineages, for unclear reasons the granulocyte precursors are most affected. The increased number of granulocytes in the bone marrow and peripheral blood, the proliferating CML progenitors, is a result of the altered differentiation.

#### **Morphology**

The peripheral blood findings are highly characteristic. The leukocyte count is elevated, usually >100,000 cells/ $\mu$ L. The circulating cells are **predominantly neutrophils, metamyelocytes, and bands** (Fig. 12-26), but basophils and eosinophils are also prominent. A small proportion of lymphocytes, **less than 5%**, can be seen in the peripheral blood. An increased number of platelets is also present, usually >1,000,000/ $\mu$ L. The bone marrow is hypercellular as a result of a hyperplasia of granulocyte precursors. Myeloblasts are usually only slightly increased, and there is frequently an increase in the number of phagocytes. The red pulp of the enlarged spleen has an appearance that resembles that of the bone marrow because of the extensive extramedullary hematopoiesis. This hyperplastic mass of

because of the extensive extramedullary hematopoiesis. This burgeoning mass of cells compromises the local blood supply, leading to splenic infarcts.

### Clinical Features



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Figure 12-26 Chronic myelogenous leukemia. Peripheral blood smear shows many mature neutrophils, some metamyelocytes.  
Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical Center

The onset of CML is usually slow, and the initial symptoms are often nonspecific (e.g., easy fatigue). Sometimes the first symptom is a dragging sensation in the abdomen, caused by the *extreme splenomegaly* condition. On occasion it may be necessary to distinguish CML from a "leukemoid reaction," a dramatic increase in white blood cells in response to infection, stress, chronic inflammation, and certain neoplasms. *The presence of the Philadelphia chromosome* is a way of distinguishing CML from leukemoid reactions (and the other chronic myeloproliferative disorders). The *alkaline phosphatase* can also be helpful, because the granulocytes in CML are almost completely mature, whereas the granulocytes in leukemoid reactions and other myeloproliferative disorders (such as PCV) are mostly immature.

The course of CML is one of slow progression. Even without treatment, the median survival is 3 years. In the early period, approximately 50% of individuals with CML enter an accelerated phase, during which there is a rapid increase in the number of white blood cells.

treatment; increasing anemia and new thrombocytopenia; the appearance of additional cytogenetic *transformation into a picture resembling acute leukemia* (i.e., blast crisis). In the remaining 50% of patients, the blast crisis is of an intermediate accelerated phase. Notably, in 30% of patients, the blast crisis is of a pre-B-cell type from a pluripotent stem cell. In the remaining 70% of patients, the blast crisis resembles AML. Less than 10% of patients have extensive bone marrow fibrosis resembling that seen in other myeloproliferative disorders, most notably myelofibrosis.

Treatment of CML is evolving rapidly. Most patients were formerly treated with palliative "gentle" chemotherapy to prevent the development of blast crisis. Bone marrow transplantation was (and remains) a definitive treatment for some patients, but it carries a high risk of death in patients without a matched donor and in the aged. The tyrosine kinase, Gleevec (imatinib mesylate), induces complete remission in a high fraction of individuals with CML, with toxicity associated with nonspecific chemotherapeutic agents. When CML sufferers have mutations in the active site of BCR-ABL that prevent the binding of imatinib mesylate; this proves to be a "non-target." Further work is needed to determine whether imatinib mesylate is curative, but it is an excellent alternative to bone marrow transplantation and has stimulated great interest in the development of other targeted therapies.

### Polycythemia Vera

The hallmark of PCV is the excessive neoplastic proliferation and maturation of erythroid, granulocytic, and megakaryocytic cells, producing a *panmyelosis*. Although platelet and granulocyte numbers are increased, the most obvious feature is the *absolute increase in red cell mass*. This must be distinguished from *relative polycythemia* (hemoconcentration). Unlike reactive forms of absolute polycythemia, PCV is associated with *low levels of erythropoietin*, a reflection of the hypersensitivity of the neoplastic clone to erythropoietin and other growth factors. In nearly all cases, PCV cells carry a particular mutation in JAK2, a tyrosine kinase that acts in the signaling pathway of the erythropoietin receptor and other growth factor receptors. This mutation, which results in a valine-to-leucine substitution at position 617, is sufficient to render cells expressing the erythropoietic receptor hypersensitive to erythropoietin. This mutation is an important part of the pathogenesis of PCV.

#### Morphology

The major anatomic changes in PCV stem from the increase in blood volume and the polycythemia. Plethoric congestion of all tissues and organs is characteristic. The spleen is frequently enlarged, and the liver contains foci of extramedullary hematopoiesis. The spleen is enlarged in about 75% of patients, because of the vascular congestion. **As a result of the increased blood volume, vascular stasis, thromboses and infarctions are common, particularly in the lower extremities and the kidneys.** Hemorrhages occur in about a third of these individuals, probably as a result of the distention of blood vessels and abnormal platelet function. They usually affect the nose, mouth, oropharynx, or brain. Although these hemorrhages may occasionally be spontaneous, they are often precipitated by some minor trauma or surgical procedure. Platelets produced from the neoplastic clone are often dysfunctional. Depending on their nature, the platelet defects can either exacerbate thrombosis or lead to abnormal bleeding. As in CML, the peripheral blood often shows a leukoerythroblastic picture.

The bone marrow is hypercellular due to the hyperplasia of erythroid, myeloid, and megakaryocytic cells. In addition, some degree of marrow fibrosis is present in 10% of patients at the time of diagnosis. As the disease progresses to myelofibrosis, where the marrow space is largely replaced by collagen and abnormal megakaryocytes.

#### Clinical Course

PCV appears insidiously, usually in late middle age. Patients are plethoric and often somewhat cyanotic. Pruritus, which can be intense, is often associated with the disease. Excessive histamine release from neoplastic basophils may contribute to *pruritus*, which can be intense. Excessive histamine release may also contribute to the *ulceration* seen in these individuals. Other complaints are referable to the thrombotic and hemorrhagic complications. *Headache, dizziness, gastrointestinal symptoms, hematemesis, and melena are common.* Because of the increased blood volume, symptomatic gout is seen in 5% to 10% of cases, and many more patients have asymptomatic hyperuricemia.

The diagnosis is usually made in the laboratory. Red cell counts range from 6 to 10 million per microliter, and the hemoglobin approaches 60%. The other myeloid lineages are also hyperproliferative: the granulocyte count can be increased, and the platelet count is often elevated.

the platelet count is often greater than 400,000 cells/mm<sup>3</sup>. The basophil count is also frequently abnormal in most cases, and giant forms and megakaryocyte fragments are seen in the blood. Abnormalities are usually affecting the brain or heart. Hepatic vein thrombosis, giving rise to the Budd-Chiari syndrome, is an uncommon but grave complication. Minor hemorrhages (e.g., epistaxis and bleeding from gums) and major hemorrhages occur in 5% to 10% of patients. In those receiving no treatment, death occurs from bleeding complications; however, if the red cell mass is maintained at near normal levels by phlebotomies, the

Prolonged survival with treatment has revealed that PCV tends to evolve to a "spent phase," during which the features of primary myelofibrosis develop. After an average interval of 10 years, 15% to 20% of patients undergo this transition, marked by creeping fibrosis in the bone marrow and a shift of hematopoiesis to the extramedullary sites. Transformation to a "blast crisis" identical to AML also occurs but much less frequently than in CMV. The use of JAK2 inhibitors is presently under consideration.

#### Myeloid Metaplasia with Primary Myelofibrosis

In this chronic myeloproliferative disorder, a "spent phase" of marrow fibrosis supervenes early in the disease course, during a period in which the peripheral blood white cell and platelet counts are elevated. As hematopoiesis shifts to the spleen, liver, and lymph nodes, extreme splenomegaly and hepatomegaly develop. Hematopoiesis becomes disordered and inefficient and, together with the marrow fibrosis, leads to moderate-to-severe anemia in most patients.

Although marrow fibrosis is characteristic, the fibroblasts that lay down the collagen are not clonal cells. Instead, marrow fibrosis is secondary to derangements confined to the hematopoietic cells, and it is believed that *marrow fibroblasts are stimulated to proliferate by platelet-derived growth factor and transforming growth factor-β* from neoplastic megakaryocytes. These two growth factors are known to be mitogenic for fibroblasts. In addition, marrow fibrosis and marked extramedullary hematopoiesis are usually evident. More advanced at diagnosis, and the clinical picture resembles that seen in other "hyperproliferative" myeloproliferative disorders.

It is of pathogenic and possibly therapeutic importance that the same JAK2 mutation that is found in primary myelofibrosis (a mutation at amino residue 617) is present in around half of the cases of primary myelofibrosis (as well as in essential thrombocythosis), findings that emphasize the extent of the overlap between these two disorders. Findings that with the same mutation have such varied clinical pictures. Perhaps the JAK2 mutation occurs in a subset of primary myelofibrosis, or the unknown mutations that promote progression to the spent phase occur much

#### Morphology

The principal site of the extramedullary hematopoiesis in myeloid metaplasia with primary myelofibrosis is the **spleen**, which is usually markedly enlarged, sometimes weighing as much as 4000 g. When splenomegaly is massive, multiple **subcapsular infarcts** are often present. The spleen contains normoblasts, granulocyte precursors, and megakaryocytes, which are often increased in their numbers and bizarre morphology. Sometimes disproportional activity of any one cell line is seen.

The **liver** is often moderately enlarged, with foci of extramedullary hematopoiesis. The **nodes** also contain foci of extramedullary hematopoiesis, but these are insufficient to cause significant enlargement.

The **bone marrow** in a typical case is **hypocellular and diffusely fibrotic**. However, in some cases the marrow can be hypercellular, with equal representation of the three major cell lines. In the latter case, megakaryocytes are often prominent and are usually dysplastic.

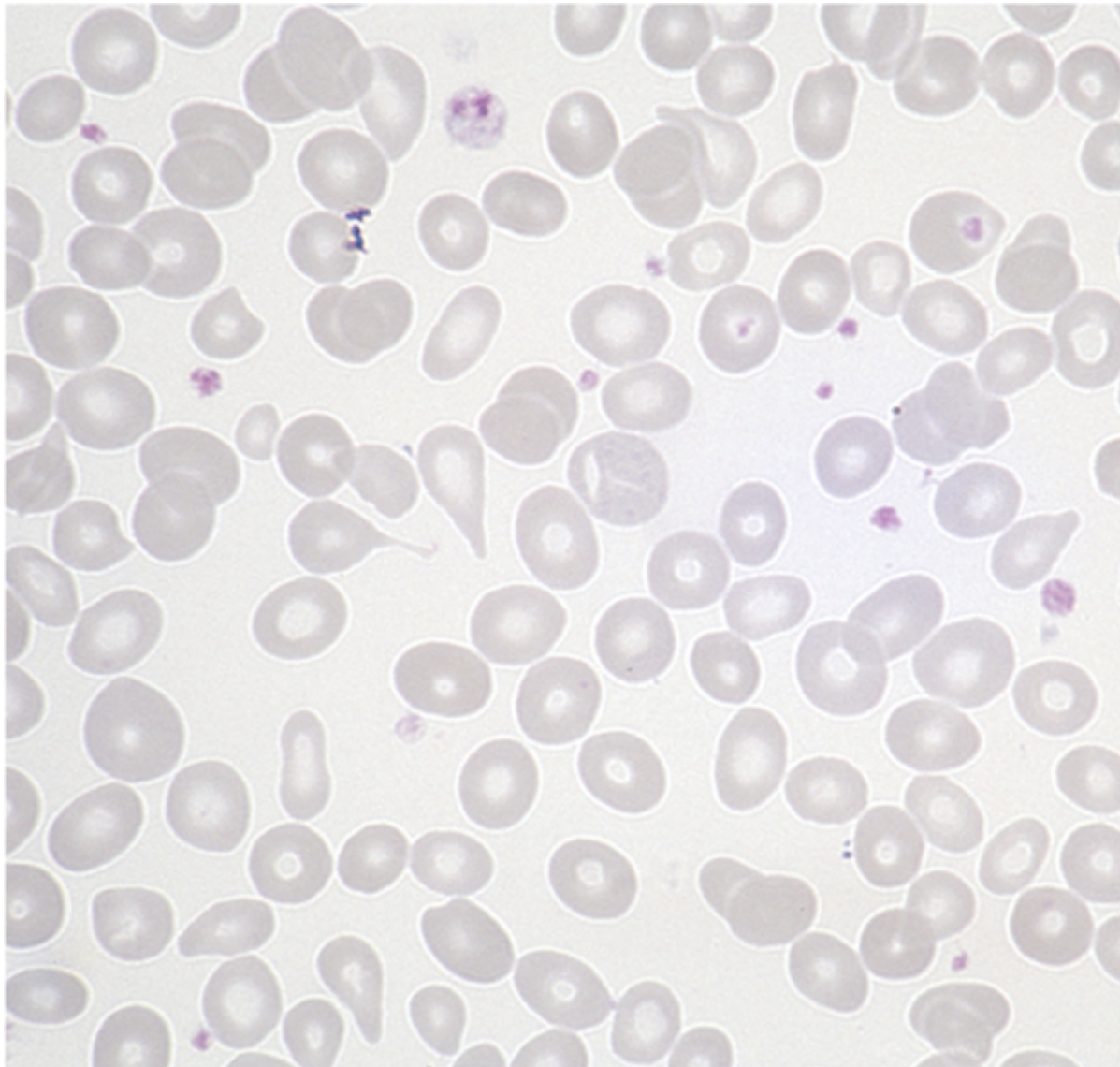
#### Clinical Course

Primary myelofibrosis can begin with a blood picture suggestive of PCV or CML, but it more commonly presents with anemia by the time it comes to clinical attention. Most patients have moderate-to-severe anemia. The white blood cell count is usually markedly elevated. Early in the disease course, the platelet count is normal or elevated, but eventually it falls. The *peripheral blood smear appears markedly abnormal* (Fig. 12-27). Red cell abnormalities include poikilocytosis (abnormal cells). Nucleated erythroid precursors are often found in the peripheral blood as well. Immature white blood cells (metamyelocytes) are also seen, and basophils are sometimes increased as well. The presence of immature white cells is referred to as leukopenic thrombocytosis. Platelets are often abnormal in size and



immature white cells is referred to as *leukoerythrocytosis*. Platelets are often abnormal in size and cases the clinical and blood picture resembles CML, but the *Ph chromosome is absent*. Because *hyperuricemia and gout* may also complicate the picture.

The outcome of this disease is variable, but the median survival time is 4 to 5 years. There is a co thrombotic and hemorrhagic episodes stemming from platelet abnormalities. Splenic infarctions and there is eventually a blast crisis resembling AML.



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Figure 12-27 Myelofibrosis with myeloid metaplasia (peripheral blood smear). Two nucleated erythroid precursor (dacyocytes) are evident. Immature myeloid cells were present in other fields. An identical picture can be seen in fibrosis.

## SUMMARY

### Myeloid Neoplasms

Myeloid tumors are mainly tumors of adults that fall into three groups.

*Acute Myelogenous Leukemias (AML):*

Collection of aggressive tumors that are comprised of immature myeloid cells (myeloblasts), which replace the marrow and suppress normal hematopoiesis. They contain diverse genetic lesions that often lead to the expression of growth factors that block myeloid cell differentiation.

***Chronic Myeloproliferative Disorders:***

Indolent tumors in which production of cells is initially increased, local and extramedullary hematopoiesis. Commonly associated with acquired mutations that lead to constitutive activation of tyrosine kinases, which mimic signal factors; treated with kinase inhibitors. Two main types are:

***Chronic Myelogenous Leukemia (CML):*** myeloid tumor arising from a hematopoietic cell; associated with chromosome rearrangements that cause the *ABL* fusion gene, which encodes a constitutively active tyrosine kinase, leading to increased hematopoiesis, particularly in the granulocytic and erythroid lineages. If untreated, inevitably progresses to a blast crisis phase that can resemble lymphoblastic leukemia. ***Polycythemia Vera:*** myeloid tumor associated with mutations that activate *JAK2*, a tyrosine kinase; causes increased red blood cell, platelet, and white cell counts; the latter is responsible for many clinical symptoms.

***Myelodysplastic Syndromes:*** group of myeloid tumors characterized by dysplasia of hematopoiesis. Most patients present with pancytopenia, and many progress to acute myeloid leukemia (AML).

***Myeloid Metaplasia with Myelofibrosis*** is the most common myelodysplastic syndrome. It is a myeloid tumor in which abnormal megakaryocytes release growth factors that stimulate reactive marrow fibroblasts to deposit collagen, and the resulting fibrotic marrow space, leading to pancytopenia and extramedullary hematopoiesis, often with massive splenomegaly.

## **Histiocytic Neoplasms**

### ***Langerhans Cell Histiocytoses***

The term *histiocytosis* is an "umbrella" designation for a variety of proliferative disorders of histiocytes. Some, such as the very rare histiocytic lymphomas, are clearly malignant neoplasms. Others, such as the Langerhans cell histiocytoses, are completely benign and reactive. Between these two extremes lies a group of relatively rare tumors, the Langerhans cell histiocytoses, which are derived from Langerhans cells. You will recall that the Langerhans cell is an immature cell found in many organs, most prominently the skin ([Chapter 5](#)).

These proliferations take on different clinical forms, but all are believed to be variations of the same process. Langerhans cells are human leukocyte antigen DR (HLA-DR) positive and express the CD1 antigen. *Birbeck granules* (dense bodies) are seen in their cytoplasm. Under the electron microscope these are seen to have a characteristic structure, with characteristic periodicity and sometimes a dilated terminal end ("tennis racket" appearance). Proliferating Langerhans cells in these disorders do not resemble their normal dendritic counterparts. The cytoplasm is vacuolated, with vesicular nuclei. This appearance is more akin to that of tissue histiocytes. The term *Langerhans cell histiocytosis* is used.

***Acute disseminated Langerhans cell histiocytosis (Letterer-Siwe disease)*** usually occurs in children, but has occasionally been seen in adults. The dominant clinical feature is the development of multifocal cutaneous lesions. Langerhans cells that grossly resemble seborrheic skin eruptions. Most of those affected have concurrent lymphadenopathy, pulmonary lesions, and, eventually, destructive osteolytic bone lesions. Extension to anemia, thrombocytopenia, and predisposition to recurrent infections such as otitis media and respiratory infections. The course of untreated disease is rapidly fatal. With intensive therapy, survival may be 5 years.

***Both unifocal and multifocal Langerhans cell histiocytosis (unifocal and multifocal eosinophilic granuloma)*** are characterized by massive accumulations of Langerhans cells, usually within the medullary cavity of bone. Histio-

erosive accumulations of Langerhans cells, usually within the medullary cavities of bones. Histiocytosis includes eosinophils, lymphocytes, plasma cells, and neutrophils. The eosinophilic component ranges from small clusters to large masses of cells. Virtually any bone in the skeletal system may be involved; the calvarium, ribs, and vertebrae. Similar lesions may be found in the skin, lungs, or stomach, either as unifocal lesions or as components of a systemic disease.

*Unifocal lesions* usually affect the skeletal system. They may be asymptomatic or cause pain and pathologic fractures. This is an indolent disorder that may heal spontaneously or be cured by local therapy.

*Multifocal Langerhans cell histiocytosis* usually affects children, who present with fever; diffuse erythema; otitis media; and frequent bouts of otitis media, mastoiditis, and upper respiratory tract infection. It may also cause mild lymphadenopathy, hepatomegaly, and splenomegaly. In about 50% of patients, involvement of the hypothalamus leads to diabetes insipidus. The combination of calvarial bone defects, diabetes insipidus, and exophthalmos is known as the *Hand-Schüller-Christian triad*. Many patients experience spontaneous regressions; others have a chronic course.



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## BLEEDING DISORDERS

These disorders are characterized clinically by abnormal bleeding, which can either be spontaneous or become evident after some inciting event (e.g., trauma or surgery). It should be recalled from the discussion in [Chapter 4](#) that the normal hemostatic response involves the blood vessel wall, the platelets, and the clotting cascade, and abnormalities in any of these three components can be associated with clinically significant bleeding. Before embarking on a discussion of disorders of coagulation, we should first review normal hemostasis and the common laboratory tests used in the evaluation of a bleeding diathesis. The various tests used in the initial evaluation of patients with bleeding disorders are as follows:

*Bleeding time.* This represents the time taken for a standardized skin puncture to stop bleeding. Measured in minutes, this procedure provides an in vivo assessment of platelet response to limited vascular injury. The reference range depends on the actual method used and varies from 2 to 9 minutes. It is abnormal when there is a defect in platelet numbers or function. Bleeding time is fraught with variability and poor reproducibility. Hence, new instrument-based assays that provide quantitative measures of platelet function are being introduced. *Platelet counts.* These are obtained on anticoagulated blood by using an electronic particle counter. The reference range is  $150 \times 10^3$  to  $450 \times 10^3$  cells/mm<sup>3</sup>. Counts outside this range must be confirmed by a visual inspection of a peripheral blood smear. *Prothrombin time (PT).* This procedure tests the adequacy of the extrinsic and common coagulation pathways. It represents the time needed for plasma to clot in the presence of an exogenously added source of tissue thromboplastin (e.g., brain extract) and Ca<sup>2+</sup> ions. A prolonged PT can result from a deficiency of factors V, VII, or X, prothrombin, or fibrinogen. *Partial thromboplastin time (PTT).* This test is designed to assess the integrity of the intrinsic and common clotting pathways. In this test the time needed for the plasma to clot in the presence of kaolin, cephalin, and calcium is measured. Kaolin serves to activate the contact-dependent factor XII, and cephalin substitutes for platelet phospholipids. Prolongation of PTT can be caused by a deficiency of factors V, VIII, IX, X, XI, or XII or prothrombin or fibrinogen or an acquired inhibitor (typically an antibody) that interferes with the intrinsic pathway.

Additional, more specialized tests are available that measure the levels of specific clotting factors, fibrinogen, and fibrin split products; assess the presence of circulating anticoagulants; and evaluate platelet function. With this overview we can return to the three important categories of bleeding disorders.

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Abnormalities of vessels can contribute to bleeding in several ways. *Increased fragility* of the vessels is associated with severe vitamin C deficiency (scurvy) ([Chapter 8](#)), systemic amyloidosis ([Chapter 5](#)), chronic glucocorticoid use, rare inherited conditions affecting the connective tissues, and a large number of infectious and hypersensitivity vasculitides. The latter include meningococcemia, infective endocarditis, the rickettsial diseases, typhoid, and Henoch-Schönlein purpura. Some of these conditions are discussed in other chapters; others are beyond the scope of this book. A hemorrhagic diathesis that is purely the result of vascular fragility is characterized by the apparently spontaneous appearance of petechiae and ecchymoses in the skin and mucous membranes (probably resulting from minor trauma). In most instances, the laboratory tests of coagulation are normal. *Bleeding can also be triggered by systemic conditions that activate or damage endothelial cells.* If severe enough, such



insults convert the vascular lining to a prothrombotic surface that activates coagulation throughout the circulatory system. Paradoxically, in such *consumptive coagulopathies* platelets and coagulation factors are used up faster than they can be replaced, and the resulting deficiencies (which are readily identified in laboratory tests of coagulation) often lead to severe bleeding.

*Deficiencies of platelets* (thrombocytopenia) are important causes of hemorrhage. They can occur in a variety of clinical settings that are discussed later. Other disorders are characterized by *qualitative defects in platelet function*. These include defects that are *acquired*, as in uremia, after [aspirin<sup>®</sup>](#) ingestion, and in certain myeloproliferative disorders, or *inherited*, as in von Willebrand disease and other rare congenital disorders. The clinical signs of inadequate platelet function include easy bruising, nosebleeds, excessive bleeding from minor trauma, and menorrhagia. The PT and PTT are normal, but *the bleeding time is prolonged*.

Bleeding diatheses based purely on a *derangement of blood clotting* differ in several respects from those resulting from defects in the vessel walls or in platelets. The PT, PTT, or both, are prolonged, whereas the bleeding time is normal. Petechiae and other evidence of bleeding from very minor surface trauma are usually absent. However, massive hemorrhage can occur subsequent to operative or dental procedures or severe trauma. Moreover, hemorrhages into areas of the body subject to trauma, such as the joints of the lower extremities, are characteristic. This category includes the hemophilias, an important group of inherited coagulation disorders.

Disseminated intravascular coagulation, one of the most common consumptive coagulopathies, presents with laboratory and clinical features related to both thrombocytopenia and coagulation factor deficiencies. Von Willebrand disease is a fairly common inherited disorder in which both platelet and (to a lesser degree) coagulation factor function are abnormal. With this as an overview, we will now turn to specific bleeding disorders.





## DISSEMINATED INTRAVASCULAR COAGULATION

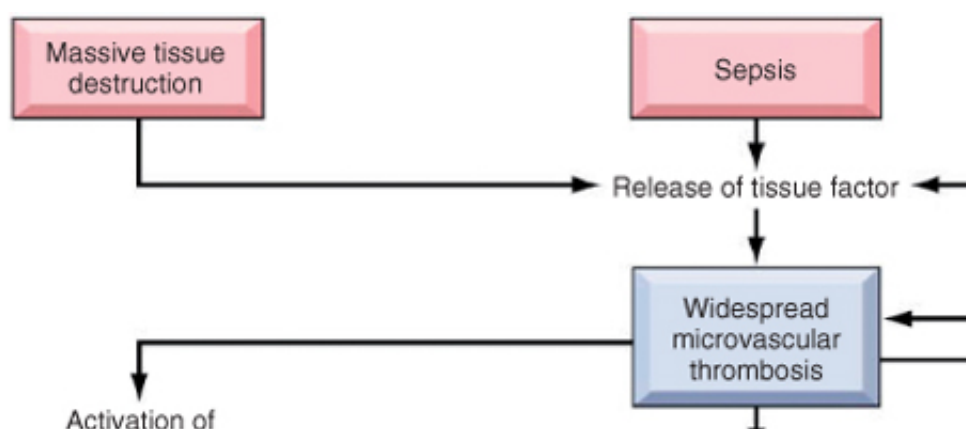
An acute, subacute, or chronic thrombohemorrhagic disorder, disseminated intravascular coagulation is a complication in a variety of diseases. *It is caused by the systemic activation of the coagulation pathway, resulting in the formation of microthrombi throughout the microcirculation. As a consequence of the widespread thromboses, there is consumption of coagulation factors and, secondarily, activation of fibrinolysis.* Thus, DIC can give rise to either tissue thromboses or to a bleeding disorder related to pathologic activation of fibrinolysis and the hemostasis (hence the term *consumptive coagulopathy*). This entity is probably a more common complication of acquired than of congenital coagulation disorders combined.

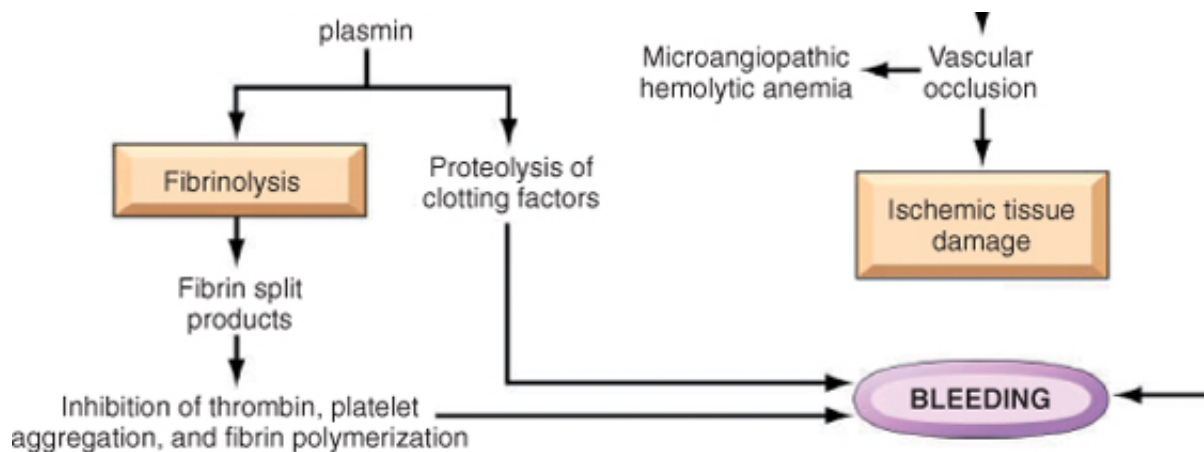
### *Etiology and Pathogenesis*

Before presenting the specific disorders associated with DIC, we will discuss in a general way the ways in which intravascular clotting can occur. Reference to earlier comments on normal blood coagulation (Chapter 11) suffices here to recall that clotting can be initiated by either of two pathways: the extrinsic pathway, which involves tissue factor (tissue thromboplastin), or the intrinsic pathway, which involves the activation of factor XII by other negatively charged substances. Both pathways lead to the generation of **thrombin**. Clotting is cleared of activated clotting factors by the mononuclear phagocytic system or by the liver, activation of protein C), and activation of fibrinolysis.

Two major mechanisms can trigger DIC: (1) the release of tissue factor or thromboplastin substance into the blood by widespread endothelial cell damage (Fig. 12-28). Thromboplastin substances can be released into the blood, for example, the placenta in obstetric complications, the cytoplasmic granules of acute promyelocytic leukemia cells. Carcinomas can also release other procoagulant substances, such as prothrombin and tumor products. Some tumors express tissue factor on the cell membrane. In gram-negative and gram-positive sepsis (DIC), endotoxins or exotoxins cause increased synthesis, surface expression, and release of tissue factor. Activated monocytes release IL-1 and tumor necrosis factor, both of which increase the expression of tissue factor. Simultaneously decrease the expression of thrombomodulin. The latter, you may recall, activates protein C. The net result is the enhanced activation of the extrinsic clotting system and the blunting of inhibitory mechanisms of coagulation.

Severe endothelial cell injury can initiate DIC by causing the release of tissue factor and by exposing subendothelial collagen, which act together to promote platelet aggregation and the activation of tissue plasminogen activator (tPA), which act together to promote platelet aggregation and the activation of tPA. Subtle endothelial damage can unleash procoagulant activity by stimulating the increased expression of tissue factor on endothelial surfaces. Widespread endothelial injury can be produced by the deposition of antigen-antibody complexes (e.g., following heat stroke or burns), or by infections (e.g., meningococci and rickettsiae). Endothelial injury is an important consequence of endotoxemia, and, not surprisingly, DIC is a frequent complication of sepsis.





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Figure 12-28 Pathophysiology of disseminated intravascular coagulation

**Table 12-12. Major Disorders Associated with Disseminated Intravascular Coagulation**

<b>Obstetric Complications</b>
Abruptio placentae
Retained dead fetus
Septic abortion
Amniotic fluid embolism
Toxemia
<b>Infections</b>
Sepsis (gram-negative and gram-positive)
Meningococcemia
Rocky Mountain spotted fever
Histoplasmosis
Aspergillosis
Malaria
<b>Neoplasms</b>
Carcinomas of pancreas, prostate, lung, and stomach
Acute promyelocytic leukemia
<b>Massive Tissue Injury</b>
Trauma
Burns
Extensive surgery
<b>Miscellaneous</b>
Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm

Several additional disorders associated with DIC are listed in Table 12-12. Of these, *DIC is most common in obstetric complications, malignancy, and major trauma (especially trauma to the brain)*. The initiating event is often interrelated. For example, in obstetric conditions, tissue factor derived from the placenta, enters the circulation; however, shock, hypoxia, and acidosis often coexist and can lead to widespread endothelial injury and releases fat and phospholipids, which can act as contact factors and thereby activate the intrinsic

Whatever the pathogenetic mechanism, DIC has two consequences. First, *there is widespread fibrin deposition*. This leads to ischemia in the more severely affected or vulnerable organs and to hemolysis as red blood cells pass through vessels narrowed by fibrin thrombi (*microangiopathic hemolytic anemia*). Second, a *bleeding tendency* develops because of consumption of platelets and clotting factors and the secondary release of plasminogen activators. Plasmin cleaves factors V and VIII, thereby reducing their concentration further. In addition, fibrinolysis creates fibrin degradation products (FDPs) that interfere with platelet aggregation and fibrin polymerization.

factors v and viii, thereby reducing their concentration further. In addition, fibrinolysis creates fibrinolytic products that inhibit platelet aggregation, have antithrombin activity, and impair fibrin polymerization, all of which contribute to the bleeding tendency (Chapter 12-28).

## Morphology

In DIC **microthrombi** are found principally in the arterioles and capillaries of the kidney and heart, but no organ is spared, and the lungs, liver, and gastrointestinal mucosa are also involved. The glomeruli contain small fibrin thrombi. These may be associated with swelling of the endothelial cells, or varying degrees of focal glomerulitis. The microthrombi lead to small infarcts in the renal cortex. In severe cases, the ischemia can destroy the glomeruli, leading to bilateral renal cortical necrosis. Involvement of the adrenal glands can produce the **Friderichsen syndrome** (Chapter 20). Microinfarcts are also commonly encountered in the brain, often surrounded by microscopic or gross foci of hemorrhage. These can give rise to bizarre changes in the brain. Similar changes are seen in the heart and often in the anterior pituitary. It has been suggested that DIC contributes to **Sheehan postpartum pituitary necrosis** (Chapter 20).

When the underlying disorder is toxemia of pregnancy, the placenta is the site of changes, including occasionally, florid degeneration of the vessel walls. Such changes are in all likelihood related to the premature loss of cytotrophoblasts and syncytiotrophoblasts that characterizes this condition.

The bleeding tendency associated with DIC is manifested not only by larger than normal hemorrhages but also by near foci of infarction but also by diffuse petechiae and ecchymoses, which can be seen on the skin and the linings of the body cavities, epicardium, endocardium, lungs, and mucosal lining of the gastrointestinal tract.

## Clinical Course

As might be imagined, depending on the balance between clotting and bleeding tendencies, the clinical course can be enormous. In general, *acute DIC (e.g., that associated with obstetric complications) is dominated by bleeding*, whereas *chronic DIC (e.g., as occurs in an individual with cancer) tends to present with symptoms related to thrombosis*. DIC occurs only in the microcirculation, although large vessels are involved occasionally. The manifestations include shock, with acute renal failure, dyspnea, cyanosis, convulsions, and coma. Most often, attention is drawn to the condition by prolonged and copious postpartum bleeding or by the presence of petechiae and ecchymoses on the skin. Laboratory evaluation shows *prolongation of PT and PTT* (resulting from depletion of platelets, clotting factors, and fibrinogen) and a low fibrinogen level in plasma.

The prognosis for patients with DIC is highly variable, and depends on the nature of the underlying disorder. In some acute cases it can be life-threatening and must be treated with heparin or the coagulants contained in fresh-frozen plasma. Conversely, in more chronic cases, the condition may be self-limiting. In either circumstance, definitive treatment must be directed at the cause of the DIC and its consequences.







## THROMBOCYTOPENIA

*Thrombocytopenia is characterized by spontaneous bleeding, a prolonged bleeding time, and a normal PT and PTT.* A platelet count of 100,000 cells/ $\mu$ L or less is generally considered to constitute thrombocytopenia. Platelet counts in the range of 20,000 to 50,000 cells/ $\mu$ L are associated with an increased risk of post-traumatic bleeding, and spontaneous bleeding becomes evident when counts fall below 20,000 cells/ $\mu$ L. Most bleeding tends to occur from small, superficial blood vessels and produces petechiae or large ecchymoses in the skin, the mucous membranes of the gastrointestinal and urinary tracts, and other sites. Larger hemorrhages into the central nervous system are a major hazard in patients with markedly depressed platelet counts.

The major causes of thrombocytopenia are listed in [Table 12-13](#). Clinically important thrombocytopenias are confined to those disorders in which there is reduced production or increased destruction of platelets. In most cases in which the cause is accelerated destruction, the bone marrow reveals a compensatory increase in the number of megakaryocytes. Hence, bone marrow examination can help to distinguish the two major categories of thrombocytopenia. It is also worth emphasizing that *thrombocytopenia is one of the most common hematologic manifestations of AIDS*. It can occur early in the course of HIV infection and has multifactorial bases, including immune complex-mediated platelet destruction, antiplatelet autoantibodies, and HIV-mediated suppression of megakaryocyte development and survival.

### Immune Thrombocytopenic Purpura

**Table 12-13. Causes of Thrombocytopenia**

<b>Decreased Production of Platelets</b>
Generalized disease of bone marrow
Aplastic anemia: congenital and acquired
Marrow infiltration: leukemia, disseminated cancer
Selective impairment of platelet production
Drug-induced: alcohol, thiazides, cytotoxic drugs
Infections: measles, HIV infection
Ineffective megakaryopoiesis
Megaloblastic anemia
Paroxysmal nocturnal hemoglobinuria
<b>Decreased Platelet Survival</b>
Immunologic destruction
Autoimmune: immune thrombocytopenic purpura, systemic lupus erythematosus
Isoimmune: post-transfusion and neonatal
Drug-associated: quinidine, heparin, sulfa compounds
Infections: infectious mononucleosis, HIV infection, cytomegalovirus infection
Nonimmunologic destruction
Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Giant hemangiomas
Microangiopathic hemolytic anemias
<b>Sequestration</b>

Immune thrombocytopenic purpura (ITP), also called idiopathic thrombocytopenic purpura, can occur in the setting of a variety of conditions and exposures (secondary ITP) or in the absence of any known risk factors (primary or idiopathic ITP). There are two clinical subtypes of primary ITP: chronic primary ITP, a relatively common disorder that tends to affect adult females between the ages of 20 and 40 years; and acute ITP, a self-limited form that is most commonly seen in children subsequent to viral infections.

*Antiplatelet immunoglobulins* directed against platelet membrane glycoproteins IIb/IIIa or Ib/IX complexes can be identified in 80% of patients with chronic ITP. The spleen is an important site of antiplatelet antibody production and the major site of destruction of the IgG-coated platelets. It is usually normal in size and shows only subtle evidence of increased platelet destruction; thus, splenic enlargement or lymphadenopathy should lead one to consider other possible diagnoses. Nonetheless, the importance of the spleen in this disorder is confirmed by the clinical benefits produced by splenectomy, which normalizes the platelet count and induces a complete remission in more than two-thirds of patients. The bone marrow usually contains increased numbers of megakaryocytes, a finding that is common to all forms of thrombocytopenia that are caused by accelerated platelet destruction. A marrow examination can be helpful in excluding marrow failure as a cause of the thrombocytopenia.

The onset of chronic ITP is insidious. Common findings include petechiae, easy bruisability, epistaxis, gum bleeding, and hemorrhages after minor trauma. Fortunately, more serious intracerebral or subarachnoid hemorrhages occur much less commonly. The diagnosis rests on the clinical features, the presence of thrombocytopenia, examination of the marrow, and the exclusion of secondary ITP. Reliable clinical tests for antiplatelet antibodies are not widely available.

### Heparin-Induced Thrombocytopenia

This special type of drug-induced thrombocytopenia merits brief mention because of its clinical importance. Moderate to severe thrombocytopenia develops in 3% to 5% of individuals treated with unfractionated heparin after 1 to 2 weeks of therapy. The disorder is caused by IgG antibodies that bind to platelet factor IV on platelet surfaces in a heparin-dependent fashion. This activates platelets and induces their aggregation, thus exacerbating the condition that heparin is used to treat—thrombosis. Both venous and arterial thromboses occur, even in the setting of marked thrombocytopenia, and can cause severe morbidity (e.g., loss of limbs because of vascular insufficiency) and death. Cessation of heparin therapy breaks the cycle of platelet activation and consumption.

### Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome

The term *thrombotic microangiopathies* encompasses a spectrum of clinical syndromes that include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). As originally defined, TTP is associated with the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from TTP by the absence of neurologic symptoms, the dominance of acute renal failure, and an onset in childhood ([Chapter 14](#)). Clinical experience has blurred these distinctions, because many adults with TTP lack one or more of the five criteria, and some patients with HUS have fever and neurologic dysfunction. *Fundamental to both of these conditions is the widespread formation of hyaline thrombi in the microcirculation that are composed primarily of dense aggregates of platelets surrounded by fibrin.* The consumption of

platelets leads to thrombocytopenia, and the narrowing of blood vessels by the platelet-rich thrombi results in a microangiopathic hemolytic anemia.

For many years the pathogenesis of TTP was enigmatic, although treatment with plasma exchange (initiated in the early 1970s) converted it from a disease that was almost uniformly fatal to one that is successfully treated in more than 80% of individuals. Recently, the underlying cause of most cases of TTP has been elucidated. In brief, *symptomatic patients are deficient in a metalloprotease called ADAMTS13*. This enzyme degrades very-high-molecular-weight multimer of vWF, and hence the absence of ADAMTS13 activity allows multimers of vWF to accumulate in plasma. Under some circumstances, these colossal vWF multimers promote platelet microaggregate formation throughout the circulation. The superimposition of an endothelial cell injury (caused by some other condition) can further promote microaggregate formation, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS13 activity can be an inherited condition, but it is more commonly caused by an acquired autoantibody that binds and inhibits the metalloprotease. TTP must be considered in any individual who presents with unexplained thrombocytopenia and microangiopathic hemolytic anemia, because the failure to make an early diagnosis can be fatal.

Although clinically similar to TTP, HUS has a different basis, because ADAMTS13 levels are normal in this disorder. HUS in children and the elderly usually occurs subsequent to infectious gastroenteritis caused by *E. coli* strain O157 : H7. This organism elaborates a Shiga-like toxin that damages endothelial cells, which initiates platelet activation and aggregation. Affected individuals often present with bloody diarrhea, which is followed a few days later by HUS. With supportive care and plasma exchange, recovery is possible, but irreversible renal damage and death can occur in more severe cases. About 10% of cases in children are not preceded by infection with Shiga toxin-producing bacteria. Some of these patients have mutations in the gene encoding complement regulatory proteins, notably factor H. Deficiency of this protein leads to uncontrolled complement activation after minor endothelial injury, resulting in thrombosis. HUS can also be seen after exposures to other factors (e.g., certain drugs, radiation therapy) that damage endothelial cells. Here the prognosis is more guarded, in part because the underlying conditions are often chronic or life-threatening.

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Although DIC and the thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenetically distinct. In TTP and HUS, unlike in DIC, activation of the coagulation cascade is not of primary importance, and thus the laboratory tests of coagulation (such as the PT and the PTT) are usually normal.



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## COAGULATION DISORDERS

These disorders result from either congenital or acquired deficiencies of clotting factors. Most congenital deficiencies, which typically affect many factors simultaneously. As was discussed in Chapter 8, von Willebrand disease, factor V deficiency, prothrombin and clotting factors VII, IX, and X, and its deficiency causes a severe coagulation defect. Factor XI deficiency causes a severe coagulation defect; the synthesis of several coagulation factors and the removal of many activated coagulation factors; the common causes of complex hemorrhagic diatheses.

*Hereditary deficiencies* have been identified for each of the coagulation factors. These deficiencies include Hemophilia A, resulting from deficiency of factor VIII, and hemophilia B (Christmas disease), resulting from deficiency of factor X, transmitted as X-linked recessive disorders, whereas most others are autosomal disorders. These include von Willebrand disease, hemophilia A, and hemophilia B are sufficiently common to warrant further consideration.

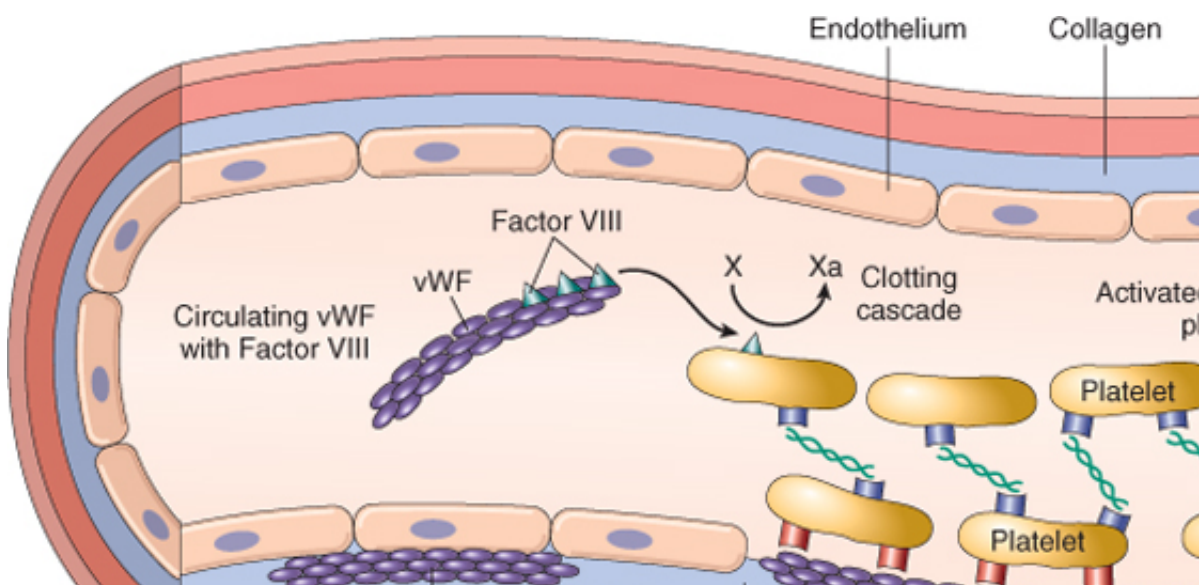
### Deficiencies of Factor VIII-vWF Complex

Hemophilia A and von Willebrand disease, two of the most common inherited disorders of bleeding, are caused by quantitative defects involving the factor VIII-vWF complex. Before we can discuss these disorders, we must first discuss the function of these proteins.

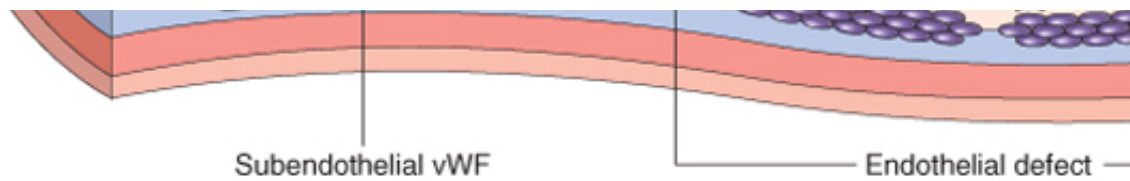
*Plasma factor VIII-vWF complex is made up of two proteins (Fig. 12-29).* One, which is required for the coagulation pathway, is called *factor VIII procoagulant protein*, or *factor VIII*. Deficiency of factor VIII is associated noncovalently with a much larger protein, vWF, that forms high-molecular-weight multimers. vWF is found normally in the plasma (in association with factor VIII), in platelet granules, and in the subendothelium, where it binds to collagen.

When endothelial cells are stripped away by trauma or injury, subendothelial vWF becomes exposed. vWF binds to platelet receptors glycoproteins Ib and IIb/IIIa (see Fig. 12-29). *The most important function of vWF is to form bridges between platelets and collagen, which is a crucial early event in the formation of a hemostatic plug.* Factor VIII is deficient in von Willebrand disease. In addition to its function in platelet adhesion, vWF also serves as a cofactor for factor VIII in the clotting cascade.

The various forms of von Willebrand disease can be characterized by immunologic techniques and by functional assays. Ristocetin (developed as an antibiotic) binds platelets and promotes the interaction between vWF and platelet glycoprotein IIb/IIIa. The binding of vWF creates interplatelet "bridges" that lead to the formation of platelet clumps that can be measured easily. Thus, ristocetin-dependent platelet agglutination serves as a useful bioassay for von Willebrand disease.







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 Figure 12-29 Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII and vWF are respectively. The two circulate as a complex in the circulation. vWF is also present in the subendothelial matrix of r coagulation cascade by activating factor X. vWF causes adhesion of platelets to subendothelial collagen, prima receptor. Ristocetin activates Gplb receptors in vitro and causes platelet aggregation

The two components of the factor VIII-vWF complex are encoded by separate genes and are synthesized by both megakaryocytes and endothelial cells. The latter are the major source of plasma. synthesized in the liver. *To summarize, the two components of factor VIII-vWF complex, synthesized; circulate in the plasma as a unit that serves to promote clotting as well as the platelet-vessel wall hemostasis.*

With this background we can turn to the discussion of diseases resulting from deficiencies of factor

### **von Willebrand Disease**

von Willebrand disease is marked by spontaneous bleeding from mucous membranes, excessive a prolonged bleeding time in the presence of a normal platelet count. In most cases it is transmitted precise incidence is difficult to estimate, because in many instances the clinical manifestations are sophisticated tests; it may well be the most common inherited bleeding disorder.

Individuals with von Willebrand disease have a compound defect involving platelet function and the factor VIII are only moderately depressed, and it is the defect in platelet function that dominates the homozygous patients with type III von Willebrand disease, the effects of factor VIII deficiency that

The classic and most common variant of *von Willebrand disease (type I) is an autosomal dominant quantity of circulating vWF*. Because vWF stabilizes factor VIII by binding to it, its deficiency causes levels, but not to levels that are clinically significant. The other, less common, varieties of von Willebrand disease are qualitative and quantitative defects in vWF. *Type II* is divided into several subtypes that are all characterized by *molecular-weight multimers of vWF*. Because these multimers are the most active form, there is a deficiency of the high-molecular-weight multimers are not synthesized, leading to a true deficiency. In type IIB, the high-molecular-weight multimers are synthesized that are rapidly removed from the circulation. These high-molecular-weight multimers are responsible for platelet aggregation (a situation reminiscent of the very-high-molecular-weight multimer aggregates). In some individuals with type IIB von Willebrand disease have chronic mild thrombocytopenia that is due to consumption.

### **Factor VIII Deficiency (Hemophilia A, Classic Hemophilia)**

Hemophilia A is the most common hereditary disease associated with serious bleeding. It is an X-linked recessive disease caused by a reduction in factor VIII activity. It primarily affects males, but much less commonly in females, presumably as a result of extremely unfavorable lyonization (inactivation of the normal X chromosome). *Approximately 30% of cases are caused by new mutations*; in the remainder, there is a positive family history. The disease is observed in individuals with a marked degree of factor VIII deficiency (activity levels of <1% of normal). The disease becomes apparent when a major hemodynamic stress supervenes, such as trauma. The varying degrees of severity are most part explained by the existence of many different causative mutations. As in the thalassemias, deletions, splice junction mutations, nonsense mutations) have been identified. In about 10% of patients, the factor VIII is normal by immunoassay, but the coagulant activity detected by bioassay is low because of a mutation that results in a functionally abnormal protein.

In all symptomatic cases there is a tendency toward easy bruising and massive hemorrhage after surgery. In addition, "spontaneous" hemorrhages are frequently encountered in regions of the body that are rich in

joints, where recurrent bleeds into the joints (*hemarthroses*) lead to progressive deformities that are *characteristically absent*. Typically, patients with hemophilia A have a prolonged PTT that is corrected by normal plasma. In approximately 15% of the most severely affected patients, replacement therapy with neutralizing antibodies against factor VIII, perhaps because factor VIII is seen as foreign in severe cases, the PTT fails to correct in mixing studies. Specific factor VIII assays are required to confirm the diagnosis.

Treatment involves infusion of factor VIII. Historically, factor VIII was prepared from human plasma free of viral diseases. As was mentioned in [Chapter 5](#), before 1985 thousands of hemophiliacs received factor VIII with HIV. Subsequently, many became seropositive and developed AIDS. The availability and wide use of more highly purified factor VIII concentrates has now eliminated the infectious risk of factor VIII.

### **Factor IX Deficiency (Hemophilia B, Christmas Disease)**

Severe factor IX deficiency is an X-linked disorder that is indistinguishable clinically from hemophilia A. The bleeding time is prolonged, and the bleeding time is normal. The diagnosis of Christmas disease (named after the first patient) is confirmed with specific assays of factor IX. It is treated by infusion of recombinant factor IX.

## **SUMMARY**

### **Bleeding Disorders**

#### *Disseminated Intravascular Coagulation:*

Syndromic in which systemic activation of the coagulation cascade by sepsis, massive tissue injury, and release of procoagulant factors from consumption of coagulation factors and platelets. The clinical picture is bleeding, vascular occlusion and tissue hypoxemia, or both. Common causes are major trauma, certain cancers, and obstetric complications.

*Immune Thrombocytopenia Purpura (ITP):* is caused by autoantibodies against platelets. It can be triggered by drugs, infections, or lymphomas, or be idiopathic. *Thrombotic Thrombocytopenic Purpura (TTP):*

Caused most commonly by acquired or inherited deficiencies of ADAMTS-13 metalloprotease that normally prevents the accumulation of very high molecular weight multimers of von Willebrand factor (vWF). Deficiency of ADAMTS-13 leads to vWF multimers, which lead to the formation of platelet-rich thrombi, particularly in the central nervous system. Manifested as thrombocytopenia and hemolytic anemia. Hemolytic Uremic Syndrome resembles TTP clinically. It is caused by deficiencies of complement regulatory protein factor H, or agents that activate the complement, such as a Shiga-like toxin elaborated by *E. coli* strain O157 : H7. The clinical picture is platelet activation, platelet aggregation, and microvasculature thrombosis.

#### *von Willebrand Disease:*

Autosomal dominant disorder caused by mutations in vWF, which is a bridging molecule between platelets and subendothelial collagen. Type 1 is a mild, moderate bleeding disorder that mimics that caused by thrombocytopenia.

*Hemophilia A* is an X-linked disorder caused by mutations in coagulation factor VIII. Patients typically present with severe bleeding into soft tissues and joints, and have a prolonged activated partial thromboplastin time (PTT). *Hemophilia B* is an X-linked disorder caused by a deficiency of factor IX; clinically, it is identical to hemophilia A.





## DISORDERS THAT AFFECT THE SPLEEN AND THYMUS

### SPLENOMEGALY

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The spleen is frequently secondarily involved in a wide variety of systemic diseases. In virtually all instances, the response of the spleen causes its enlargement (splenomegaly), which produces a set of stereotypical signs and symptoms. Evaluation of splenomegaly is a common clinical problem that is aided considerably by knowledge of the usual limits of the splenic enlargement that is seen in the context of specific disorders. It would be erroneous to attribute enlargement of the spleen into the pelvis to vitamin B<sub>12</sub> deficiency, or to entertain a diagnosis of CML in the absence of significant splenomegaly. As an aid to diagnosis, then, we present the following list of disorders, classified according to the degree of splenomegaly that is characteristically produced:

- A. Massive splenomegaly (weight more than 1000 gm)
  - 1. Chronic myeloproliferative disorders (chronic myeloid leukemia, myeloid metaplasia with myelofibrosis)
  - 2. Chronic lymphocytic leukemia
  - 3. Hairy cell leukemia
  - 4. Lymphomas
  - 5. Malaria
  - 6. Gaucher disease
  - 7. Primary tumors of the spleen (rare)
- B. Moderate splenomegaly (weight 500-1000 gm)
  - 1. Chronic congestive splenomegaly (portal hypertension or splenic vein obstruction)
  - 2. Acute leukemias (inconstant)
  - 3. Hereditary spherocytosis
  - 4. Thalassemia major
  - 5. Autoimmune hemolytic anemia
  - 6. Amyloidosis
  - 7. Niemann-Pick disease
  - 8. Langerhans histiocytosis
  - 9. Chronic splenitis (especially with infective endocarditis)
  - 10. Tuberculosis, sarcoidosis, typhoid
  - 11. Metastatic carcinoma or sarcoma
- C. Mild splenomegaly (weight <500 gm)
  - 1. Acute splenitis
  - 2. Acute splenic congestion
  - 3. Infectious mononucleosis
  - 4. Miscellaneous acute febrile disorders, including septicemia, SLE, and intra-abdominal infections

The microscopic changes associated with these diseases need not be described here, because they have been discussed in the relevant sections of this and other chapters.

An enlarged spleen often removes excessive numbers of one or more of the formed elements of blood, resulting in anemia, leukopenia, or thrombocytopenia. This is referred to as *hypersplenism*, a state that can be associated with many of the diseases affecting the spleen listed previously. In addition, platelets are particularly susceptible to sequestration in the

...more prominently in splenomegaly, platelets are particularly susceptible to sequestration in the interstices of the red pulp; as a result, thrombocytopenia is more prevalent and severe in individuals with splenomegaly than are anemia or neutropenia.



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## SPLENOMEGALY

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  - 5. Malaria
  - 6. Gaucher disease
  - 7. Primary tumors of the spleen (rare)
- B. Moderate splenomegaly (weight 500-1000 gm)
  - 1. Chronic congestive splenomegaly (portal hypertension or splenic vein obstruction)
  - 2. Acute leukemias (inconstant)
  - 3. Hereditary spherocytosis
  - 4. Thalassemia major
  - 5. Autoimmune hemolytic anemia
  - 6. Amyloidosis
  - 7. Niemann-Pick disease
  - 8. Langerhans histiocytosis
  - 9. Chronic splenitis (especially with infective endocarditis)
  - 10. Tuberculosis, sarcoidosis, typhoid
  - 11. Metastatic carcinoma or sarcoma
- C. Mild splenomegaly (weight <500 gm)
  - 1. Acute splenitis
  - 2. Acute splenic congestion
  - 3. Infectious mononucleosis
  - 4. Miscellaneous acute febrile disorders, including septicemia, SLE, and intra-abdominal infections

The microscopic changes associated with these diseases need not be described here, because they have been discussed in the relevant sections of this and other chapters.

An enlarged spleen often removes excessive numbers of one or more of the formed elements of blood, resulting in anemia, leukopenia, or thrombocytopenia. This is referred to as *hypersplenism*, a state that can be associated with many of the diseases affecting the spleen listed previously. In addition, platelets are particularly susceptible to sequestration in the interstices of the red pulp; as a result, thrombocytopenia is more prevalent and severe in individuals with splenomegaly than are anemia or neutropenia.

..... that experience, that are aimed at responsiveness.



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## DISORDERS OF THE THYMUS

As is well known, the thymus is a central lymphoid organ that has a crucial role in T-cell differentiation. It is not surprising, therefore, that the thymus can be involved by lymphomas, particularly those of T-cell lineage, which were discussed earlier in this chapter. Here we will focus on the two most frequent (albeit uncommon) disorders of the thymus: thymic hyperplasia and thymoma.

### Thymic Hyperplasia

Hyperplasia of the thymus is often associated with the appearance of lymphoid follicles, or germinal centers, within the medulla. These germinal centers contain reactive B cells, which are normally present in only low numbers in the thymus. Thymic follicular hyperplasia is present in most patients with myasthenia gravis and is sometimes also found in other autoimmune diseases, such as SLE and rheumatoid arthritis. The relationship between the thymus and myasthenia gravis is discussed in [Chapter 21](#). Significantly, removal of the hyperplastic thymus is often beneficial early in the disease.

### Thymoma

The term *thymoma* is restricted to tumors in which epithelial cells constitute the neoplastic element. Scant or abundant precursor T cells (thymocytes) are present in these tumors, but these are non-neoplastic. Several classification systems for thymoma have been proposed on the basis of cytologic and biologic criteria. One simple and clinically useful classification is as follows:

Benign or encapsulated thymoma: cytologically and biologically benign  
Malignant thymoma

Type I: cytologically benign but biologically aggressive and capable of local invasion and, rarely, distant spread  
Type II, also called *thymic carcinoma*: cytologically malignant with all of the features of cancer and comparable behavior

### Morphology

Macroscopically, thymomas are lobulated, firm, gray-white masses up to 15 to 20 cm in longest dimension. Most appear encapsulated, but in 20% to 25% there is apparent penetration of the capsule and infiltration of perithymic tissues and structures.

Microscopically, virtually all thymomas are made up of a mixture of epithelial cells and a variable infiltrate of non-neoplastic thymocytes. The relative proportions of the epithelial and lymphocytic components are of little significance. In **benign thymomas** the epithelial cells are spindled or elongated and resemble those that normally populate the medulla. As a result, these are sometimes referred to as **medullary thymomas**. In other tumors there is an admixture of the plumper, rounder, cortical-type epithelial cells; this pattern is sometimes referred to as a **mixed thymoma**. The medullary and mixed patterns account for 60% to 70% of all thymomas.

**Malignant thymoma type I** is a tumor that is cytologically bland but locally invasive. These tumors occasionally (and unpredictably) metastasize and account for 20% to 25% of all thymomas. They are composed of varying proportions of epithelial cells and reactive

thymocytes; the epithelial cells usually resemble those that are normally found in the cortex, in that they have abundant cytoplasm and rounded vesicular nuclei. The neoplastic epithelial cells often form palisades around blood vessels. Sometimes spindled epithelial cells are present as well. **The critical distinguishing feature is the penetration of the capsule and the invasion of surrounding structures.**

Malignant thymoma type II is perhaps better thought of as a form of **thymic carcinoma**. These represent about 5% of thymomas and, in contrast to the type I malignant thymomas, are malignant cytologically. Macroscopically, they are usually fleshy, obviously invasive masses sometimes accompanied by metastases to such sites as the lungs. Most resemble either poorly or well-differentiated **squamous cell carcinomas**. The next most common malignant pattern is **lymphoepithelioma-like carcinoma**, which is composed of anaplastic cortical-type epithelial cells mixed with large numbers of benign thymocytes. Tumors of this type are more common in Asian populations and sometimes contain the EBV genome.

### *Clinical Features*

All thymomas are rarities, the malignant more so than the benign. They may arise at any age but typically occur in middle adult life. In a large series, about 30% were asymptomatic; 30% to 40% produced local manifestations such as a mass demonstrable on computed tomography in the anterosuperior mediastinum associated with cough, dyspnea, and superior vena caval syndrome; and the remainder were associated with some systemic disease, principally myasthenia gravis. Fifteen to 20% of patients with this disorder have a thymoma. Removal of the tumor often leads to improvement in the neuromuscular disorder. Additional associations with thymomas include hypogammaglobulinemia, SLE, pure red cell aplasia, and nonthymic cancers.

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## 13 The Lung

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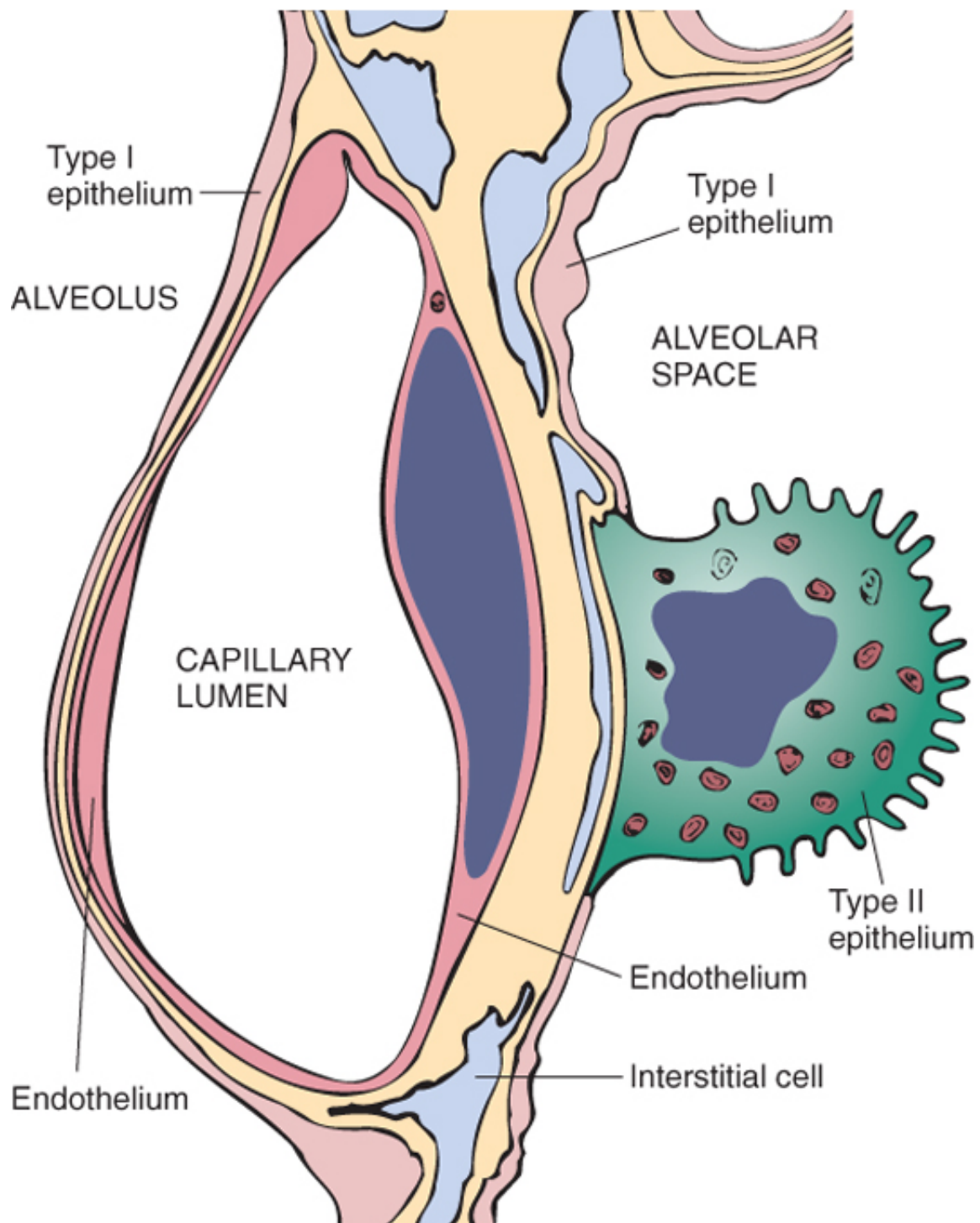


Figure 13-1 Microscopic structure of the alveolar wall. Note that the basement membrane (*yellow*) is thin on one side and widened where it is continuous with the interstitial space. Portions of interstitial cells are shown.

The major function of the lung is to excrete carbon dioxide from blood and replenish oxygen. Developmentally, the respiratory system is an outgrowth from the ventral wall of the foregut. The midline trachea develops two lateral outpocketings, the lung buds. The right lung bud eventually divides into three main bronchi, and the left into two main bronchi, thus giving rise to three lobes on the right and two on the left. The main right and left bronchi branch dichotomously, giving rise to progressively smaller airways, termed *bronchioles*, which are distinguished from bronchi by the lack of cartilage and submucosal glands within their walls. Additional branching of bronchioles leads to *terminal bronchioles*; the part of the lung distal to the terminal bronchiole is called an *acinus*. Pulmonary acini are composed of *respiratory bronchioles* (emanating from the terminal bronchiole) that proceed into *alveolar ducts*, which immediately branch into *alveolar sacs*, the blind ends of the respiratory passages, whose walls are formed entirely of *alveoli*, the ultimate site of gas exchange. The microscopic structure of the alveolar walls (or alveolar septa) consists, from blood to air, of the following (Fig. 13-1):

The capillary endothelium, a basement membrane and surrounding interstitial tissue separating the endothelium from the alveolar lining epithelium. The pulmonary interstitium, composed of fine elastic fibers, small bundles of collagen, a few fibroblast-like cells, smooth muscle cells, mast cells, and rare mononuclear cells, is most prominent in thicker portions of the alveolar septum. Alveolar epithelium, which contains a continuous layer of two principal cell types: flattened, platelike type I pneumocytes covering 95% of the alveolar surface and rounded type II pneumocytes. The latter cells are the source of pulmonary surfactant and are the main cell type involved in repair of alveolar epithelium in the wake of damage to type I pneumocytes. The alveolar walls are not solid but are perforated by numerous pores of Kohn, which permit passage of bacteria and exudates between adjacent alveoli. Alveolar macrophages, mononuclear cells of phagocytic lineage, usually lie free within the alveolar space. Often these macrophages contain phagocytosed carbon particles.

Obviously, opportunities for disease in this important organ system are legion. A common approach in the study of lung pathology, and one that provides the framework for this chapter, is to organize lung diseases into those affecting (1) the airways, (2) the interstitium, and (3) the pulmonary vascular system. This division into discrete compartments is, of course, deceptively neat. In reality, disease in one compartment is generally accompanied by alterations of morphology and function in another. We begin our discussion with atelectasis, because it can complicate many primary lung disorders.



## ATELECTASIS (COLLAPSE)

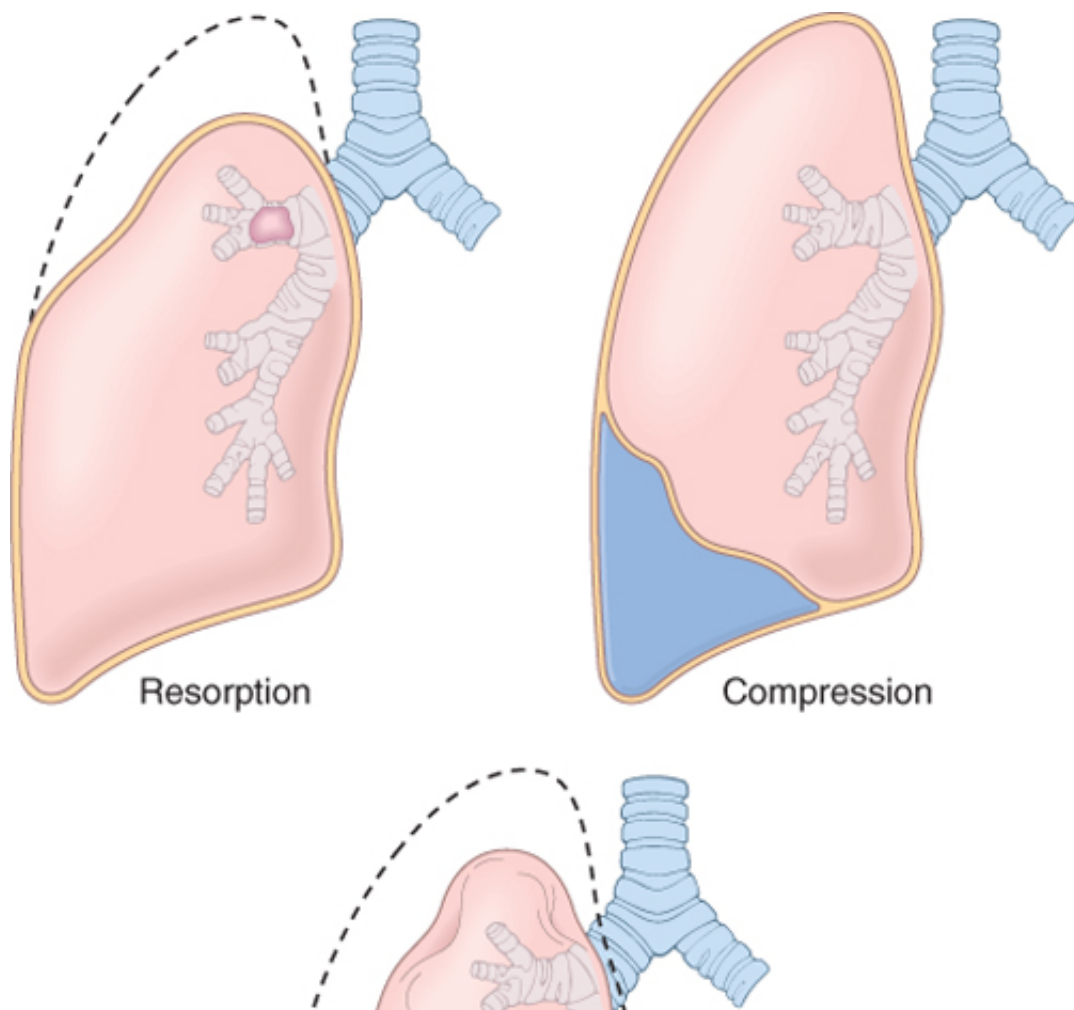
Atelectasis, also known as collapse, is loss of lung volume caused by *inadequate expansion of airspaces*. It results in shunting of inadequately oxygenated blood from pulmonary arteries into veins, thus giving rise to a ventilation-perfusion imbalance and hypoxia. On the basis of the underlying mechanism or the distribution of alveolar collapse, atelectasis is classified into three forms (Fig.13-2).

### *Resorption Atelectasis*

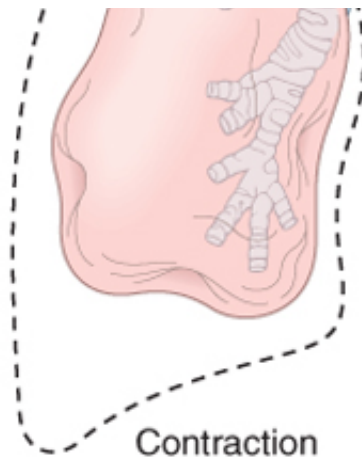
Resorption atelectasis occurs when an obstruction prevents air from reaching distal airways. The air already present gradually becomes absorbed, and alveolar collapse follows. Depending on the level of airway obstruction, an entire lung, a complete lobe, or one or more segments may be involved. The most common cause of resorption collapse is obstruction of a bronchus by a mucous or mucopurulent plug. This frequently occurs postoperatively but may also complicate bronchial asthma, bronchiectasis, chronic bronchitis, or the aspiration of foreign bodies, particularly in children.

### *Compression Atelectasis*

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Figure 13-2 Various forms of atelectasis in adults.

Compression atelectasis (sometimes called *passive* or *relaxation atelectasis*) is usually associated with accumulations of fluid, blood, or air within the pleural cavity, which mechanically collapse the adjacent lung. This is a frequent occurrence with pleural effusions, caused most commonly by congestive heart failure (CHF). Leakage of air into the pleural cavity (pneumothorax) also leads to compression atelectasis. Basal atelectasis resulting from the elevated position of the diaphragm commonly occurs in bedridden patients, in patients with ascites, and in patients during and after surgery.

#### *Contraction Atelectasis*

Contraction (or *cicatrization*) atelectasis occurs when either local or generalized fibrotic changes in the lung or pleura hamper expansion and increase elastic recoil during expiration.

Atelectasis (except that caused by contraction) is potentially reversible and should be treated promptly to prevent hypoxemia and superimposed infection of the collapsed lung.



## ACUTE LUNG INJURY

The term *acute lung injury* encompasses a spectrum of pulmonary lesions (endothelial and epithelial conditions). Clinically, acute lung injury manifests as (1) the acute onset of dyspnea, (2) decreased compliance, (3) development of bilateral pulmonary infiltrates on radiographs, and (4) absence of clinical evidence of heart failure. Since the pulmonary infiltrates in acute lung injury are usually caused by damage to the alveolar capillary membrane, they represent an example of *noncardiogenic pulmonary edema*. Acute severe *acute respiratory distress syndrome*, described below.

### Acute Respiratory Distress Syndrome (ARDS)

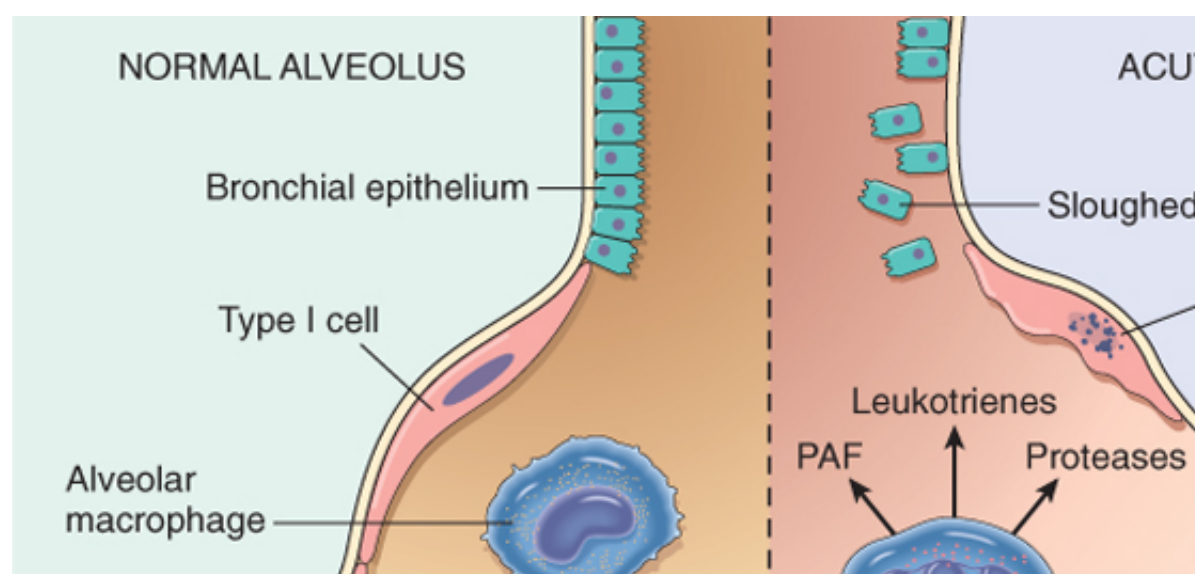
ARDS is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage. There is respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy. The histologic manifestation of ARDS in the lungs is known as *diffuse alveolar damage*. It occurs in various clinical settings and is associated with either direct injury to the lung or indirect injury in the setting of systemic disease.

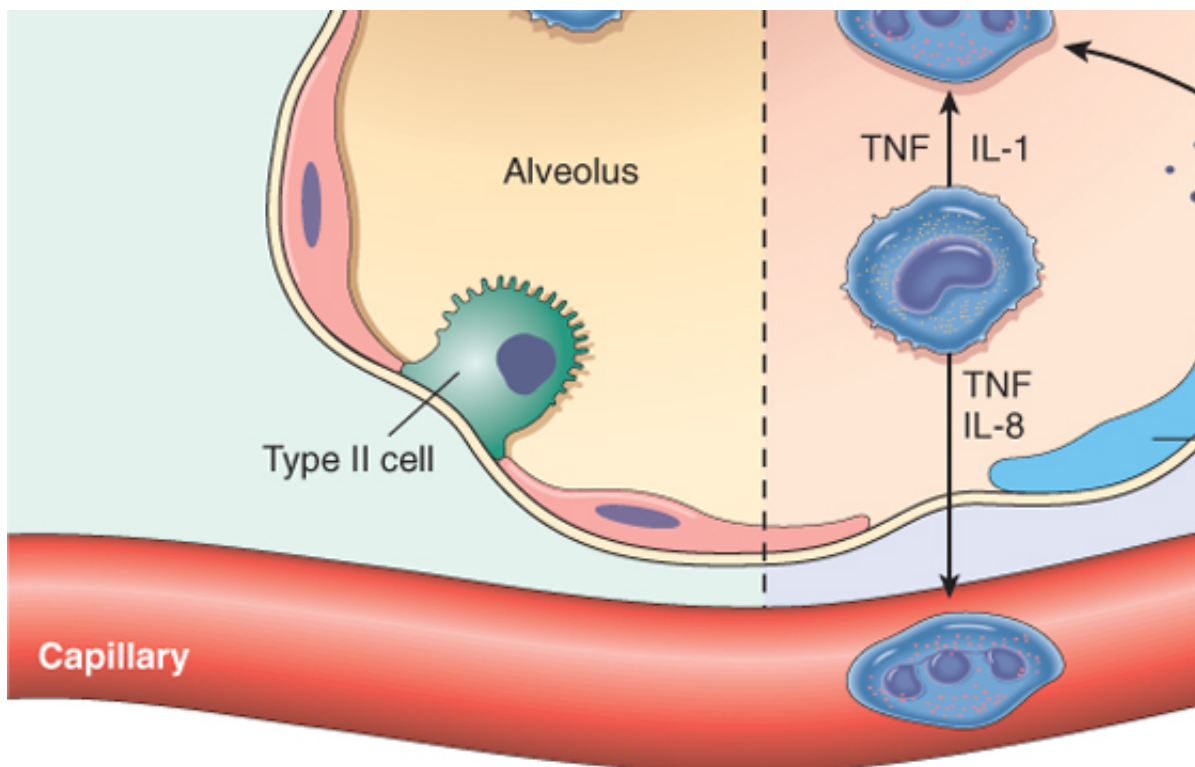
#### Pathogenesis

**Table 13-1. Clinical Disorders Associated with the Development of Acute Respiratory Distress Syndrome**

Direct Lung Injury	Indirect Lung Injury
<b>Common Causes</b>	
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with multiple fractures
<b>Uncommon Causes</b>	
Pulmonary contusion	Cardiopulmonary bypass
Fat embolism	Acute pancreatitis
Near-drowning	Drug overdose
Inhalational injury	Transfusion of blood products
Reperfusion injury after lung transplantation	Uremia

Modified from Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334, 2000.





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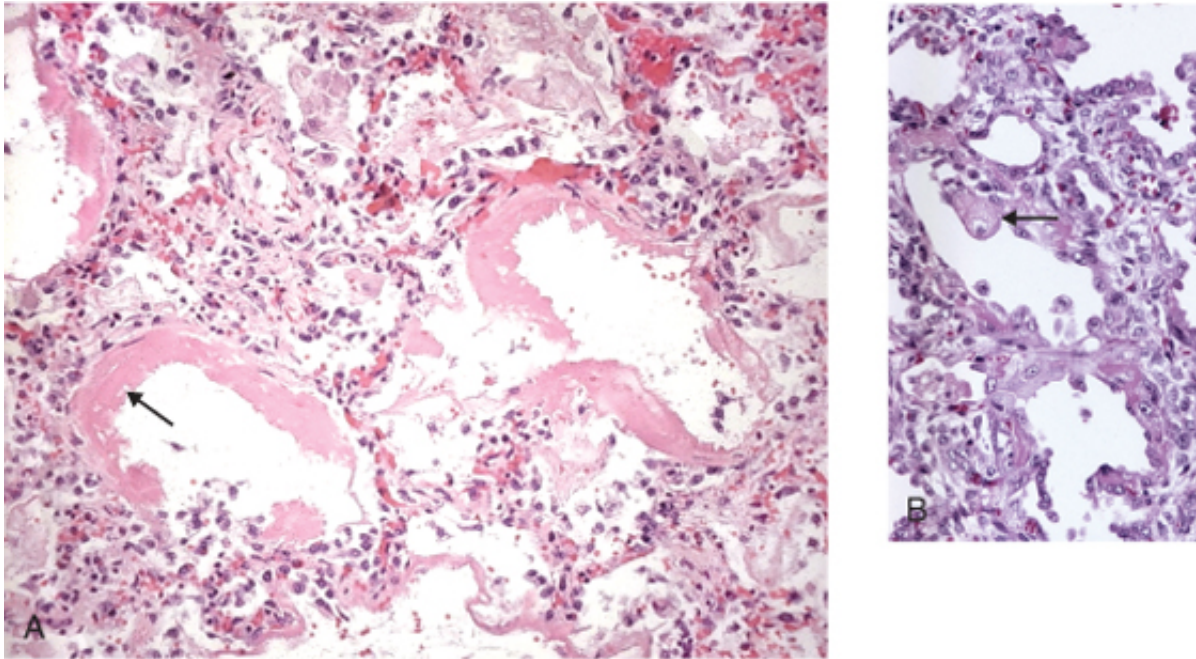
Figure 13-3 The normal alveolus (*left*) compared with the injured alveolus in the early phase of acute lung injury and the influence of proinflammatory cytokines such as IL-8, IL-1, and TNF (released by macrophages), neutrophils in the microvasculature, followed by margination and egress into the alveolar space, where they undergo activation. Activation is mediated by leukotrienes, oxidants, proteases, and platelet-activating factor (PAF), which contribute to local tissue damage, surfactant inactivation, and hyaline membrane formation. Subsequently, the release of macrophage-derived fibroblast growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor (PDGF) stimulate fibroblast growth and collagen deposition associated with fibrosis. Ware LB, Matthay MA: The acute respiratory distress syndrome. *N Engl J Med* 34

The alveolar capillary membrane is formed by two separate barriers: the microvascular endothelium and the alveolar epithelium. *the integrity of this barrier is compromised by either endothelial or epithelial injury, or, more commonly, by a combination of both.* Damage to the alveolar capillary membrane include increased vascular permeability and alveolar edema, and widespread surfactant abnormalities caused by damage to type II pneumocytes (Fig. 13-3). Although the pathogenesis of acute lung injury and ARDS remains an area of active investigation, recent work suggests that it is characterized by an *imbalance of pro-inflammatory and anti-inflammatory mediators.* The most proximate signals leading to the inflammatory response are not yet understood. However, *nuclear factor  $\kappa$ B* (NF- $\kappa$ B), a transcription factor that is regulated under normal conditions, has emerged as a likely candidate shifting the balance in favor of inflammation. Within minutes after an acute insult, there is increased synthesis of interleukin 8 (IL-8), a potent neutrophil chemoattractant for pulmonary macrophages. Release of this and similar compounds, such as IL-1 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), lead to neutrophil activation, and pulmonary microvascular sequestration and activation of neutrophils. *Neutrophils are central to the pathogenesis of ARDS.* Histologic examination of lungs early in the disease process shows neutrophils in the vascular space, the interstitium, and the alveoli. Activated neutrophils release a variety of products (including reactive oxygen species, activating factor, and leukotrienes) that cause damage to the alveolar epithelium and maintain the assault on the endothelium and epithelium perpetuate vascular leakiness and loss of surfactant that leads to alveolar collapse. It should be noted that the destructive forces unleashed by neutrophils can be counteracted by anti-inflammatory mediators (antiproteases, antioxidants, and anti-inflammatory cytokines (e.g. IL-10) that are upregulated by protective factors. The balance between the destructive and protective factors that determines the degree of tissue injury.

### Morphology

In the **acute phase of ARDS** the lungs are dark red, firm, airless, and heavy. Microscopic findings include capillary congestion, necrosis of alveolar epithelial cells, interstitial and intra-alveolar hemorrhage, and (particularly with sepsis) collections of neutrophils in capillaries.

finding is the presence of **hyaline membranes**, particularly lining the distended alveoli. Such membranes consist of fibrin-rich edema fluid admixed with remnants of necrotic debris. The picture is remarkably similar to that seen in respiratory distress syndrome in the newborn. In the **organizing stage** there is marked proliferation of type II pneumocytes in an attempt to reline the alveolar lining. Resolution is unusual; more commonly there is organization of the fibrin into resultant intra-alveolar fibrosis. Marked thickening of the alveolar septa ensues, caused by proliferation of interstitial cells and deposition of collagen.



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Figure 13-4 **A**, Diffuse alveolar damage in acute lung injury and ARDS. Some alveoli are collapsed; others are distended by hyaline membranes (arrow). **B**, In the healing stage there is resorption of hyaline membranes with thickened alveolar septa containing collagen. Numerous atypical type II pneumocytes are seen at this stage (arrows), associated with the organizing process.

### Clinical Course

Approximately 85% of patients develop the clinical syndrome of acute lung injury or ARDS within 7 days of the inciting event. The prognosis of ARDS is grim, and mortality rates have historically approached 100%. Despite improvements in supportive care, the mortality rate among the 150,000 ARDS cases seen yearly is still about 60%. Predictors of poor outcome include the underlying bacteremia (sepsis), and the development of multisystem organ failure (especially cardiac, renal, or hepatic). Patients who survive the acute stage, diffuse interstitial fibrosis may occur and continue to compromise respiratory function. Patients who survive the acute insult and are spared the chronic sequela, normal respiratory function returns.

### SUMMARY

**ARDS** ARDS is a clinical syndrome of progressive respiratory insufficiency caused by direct or indirect damage in the setting of sepsis, severe trauma, and diffuse pulmonary infection. It is characterized by an imbalance of pro- and anti-inflammatory mediators causing acute inflammation of the alveolar epithelium and capillary endothelium. Neutrophils and their products have a central role in the pathogenesis of ARDS. The characteristic histologic picture is that of alveolar necrosis, accumulation of neutrophils, and presence of hyaline membranes.





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## OBSTRUCTIVE VERSUS RESTRICTIVE PULMONARY DISEASES

Diffuse pulmonary diseases can be classified in two categories: (1) obstructive disease (airway disease), characterized by limitation of airflow usually resulting from an increase in resistance caused by partial or complete obstruction at any level, and (2) restrictive disease, characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.

*The major diffuse obstructive disorders are emphysema, chronic bronchitis, bronchiectasis, and asthma.* In patients with these diseases, total lung capacity and forced vital capacity (FVC) are either normal or increased, and the hallmark is a decreased expiratory flow rate, usually measured by forced expiratory volume at 1 second (FEV<sub>1</sub>). Thus, *the ratio of FEV<sub>1</sub> to FVC is characteristically decreased.* Expiratory obstruction may result either from anatomic airway narrowing, classically observed in asthma, or from loss of elastic recoil, characteristic of emphysema.

In contrast, in *diffuse restrictive diseases*, FVC is reduced and the expiratory flow rate is normal or reduced proportionately. Hence, *the ratio of FEV<sub>1</sub> to FVC is near normal.* The restrictive defect occurs in two general conditions: (1) *chest wall disorders in the presence of normal lungs* (e.g., severe obesity, diseases of the pleura, and neuromuscular disorders, such as the Guillain-Barré syndrome [[Chapter 23](#)], that affect the respiratory muscles) and (2) *acute or chronic interstitial lung diseases*. The classic acute restrictive disease is ARDS, discussed above. *Chronic restrictive diseases* include the pneumoconioses (see below), interstitial fibrosis of unknown etiology, and most of the infiltrative conditions (e.g., sarcoidosis).

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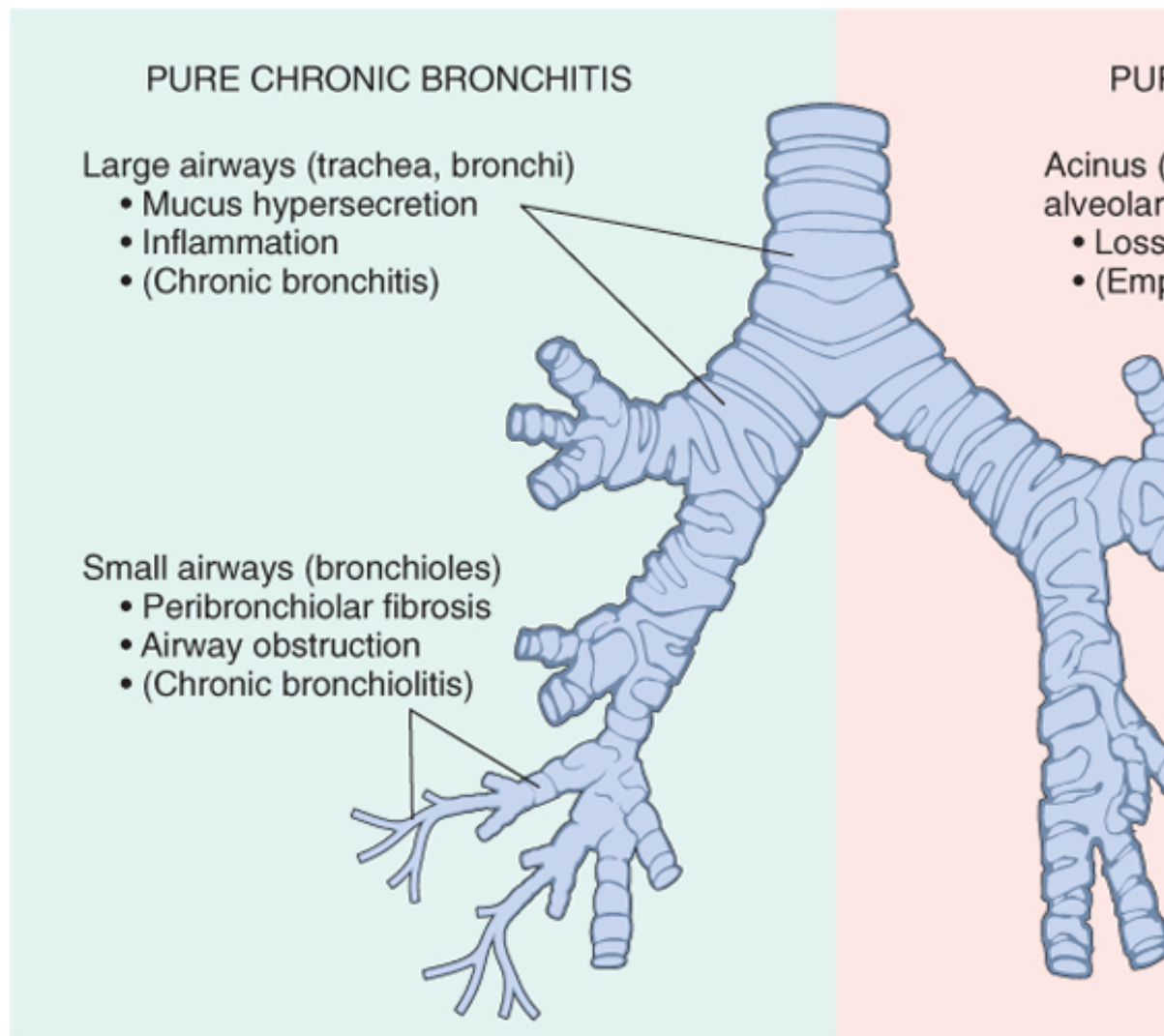
**Table 13-2. Disorders Associated with Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease**

Anatomic Major Pathologic				
Clinical Term	Site	Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucus gland hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hyperplasia, excessive mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Airspace enlargement, wall destruction	Tobacco smoke	Dyspnea
Small-airway disease, bronchiolitis*	Bronchiole	Inflammatory scarring, obliteration of bronchioles	Tobacco smoke, air pollutants	Cough, dyspnea

\*A feature of chronic bronchitis (see text).



## OBSTRUCTIVE PULMONARY DISEASE



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Figure 13-5 Anatomic distribution of pure chronic bronchitis and pure emphysema. In chronic bronchitis the small airway obstruction, while the large-airway disease is primarily responsible for the muc

In their prototypal forms, these individual disorders—emphysema, chronic bronchitis, asthma, and COPD—have distinct anatomic and clinical characteristics (Table 13-2). The relationship between chronic bronchitis and emphysema, and the lack of precise definitions has helped bring some order to what was once chaos. At the outset, it should be clear that *emphysema is morphologic, whereas chronic bronchitis is defined on the basis of clinical features*. First, the clinical features of chronic bronchitis are recurrent cough with excessive mucus secretion. Second, the anatomic distribution is also different: chronic bronchitis involves the large and small airways (the latter component has been called *chronic bronchiolitis* to indicate the involvement of the small airways), whereas emphysema is restricted to the *acinus* (Fig. 13-5). Although chronic bronchitis may exist without emphysema, pure emphysema may occur (particularly in patients with inherited  $\alpha_1$ -antitrypsin deficiency, see below). This is almost certainly because one extrinsic trigger—cigarette smoking, especially long-term, heavy smoking—is the common underlying theme in both disorders. Given their propensity to coexist, emphysema and chronic bronchitis are often

together under the rubric of *chronic obstructive pulmonary disease (COPD)*. COPD affects more than 16 million people in the United States and is the fourth leading cause of death in this country. The primarily *irreversible* airflow obstruction of COPD, which, as discussed later, is characterized largely by *reversible* airflow obstruction.

## Emphysema

Emphysema is characterized by *abnormal permanent enlargement of the airspaces* distal to the terminal bronchioles, with *destruction of their walls* without obvious fibrosis. There are several conditions in which enlargement of the airspaces occurs; this is more correctly called *overinflation*. For example, the distention of airspaces in the lung after pneumonectomy is compensatory overinflation rather than emphysema.

### Types of Emphysema

Emphysema is classified according to its *anatomic distribution* within the *lobule*; recall that the acinus is the terminal part of a bronchiole, and a cluster of three to five acini is called a *lobule*. There are four major types of emphysema: (1) centriacinar, (2) panacinar, (3) distal acinar, and (4) irregular. Only the first two cause clinically significant airway obstruction, with panacinar disease being 20-fold more common than centriacinar disease.

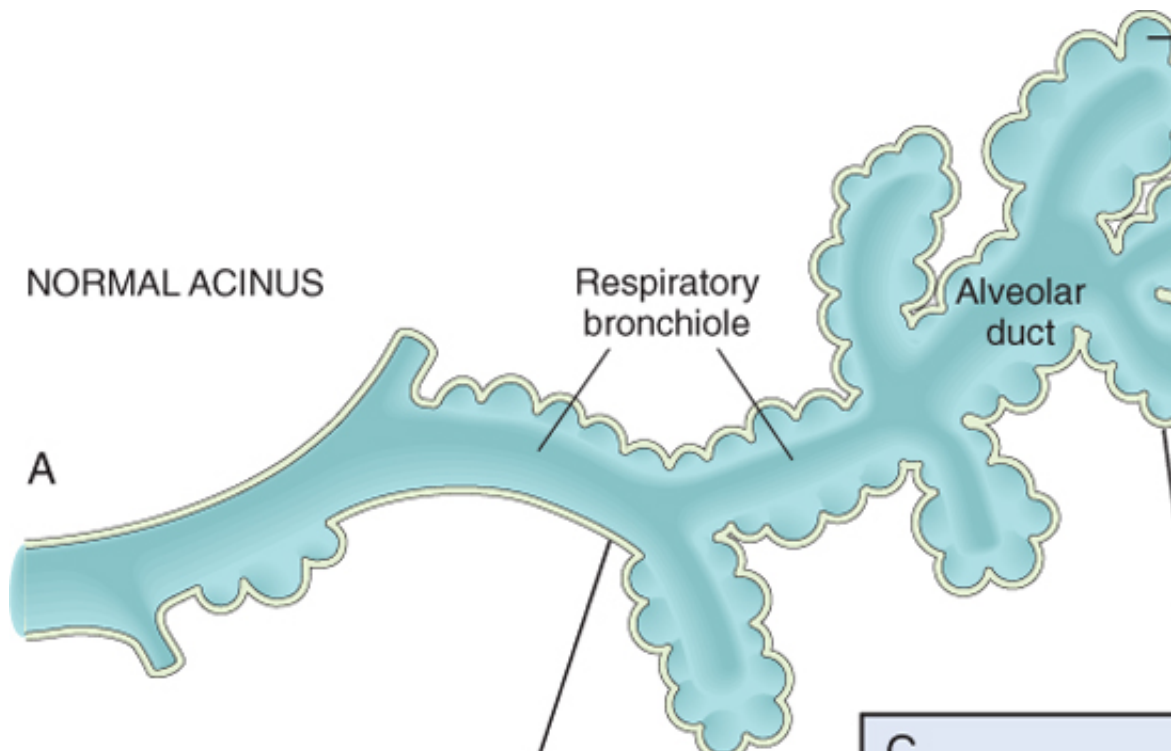
#### Centriacinar (Centrilobular) Emphysema

The distinctive feature of this type of emphysema is the pattern of involvement of the lobules: the central parts of the lobules, which are formed by respiratory bronchioles, are affected, while distal alveoli are spared. Thus, both emphysema and normal alveoli are present within the same acinus and lobule (Fig. 13-6B). The lesions are more common and severe in the upper lung segments. In severe centriacinar emphysema the distal acinus also becomes involved, and so, as the disease progresses, emphysema becomes difficult. This type of emphysema is most commonly seen as a consequence of cigarette smoking, but it can also occur in people who do not have congenital deficiency of  $\alpha_1$ -antitrypsin.

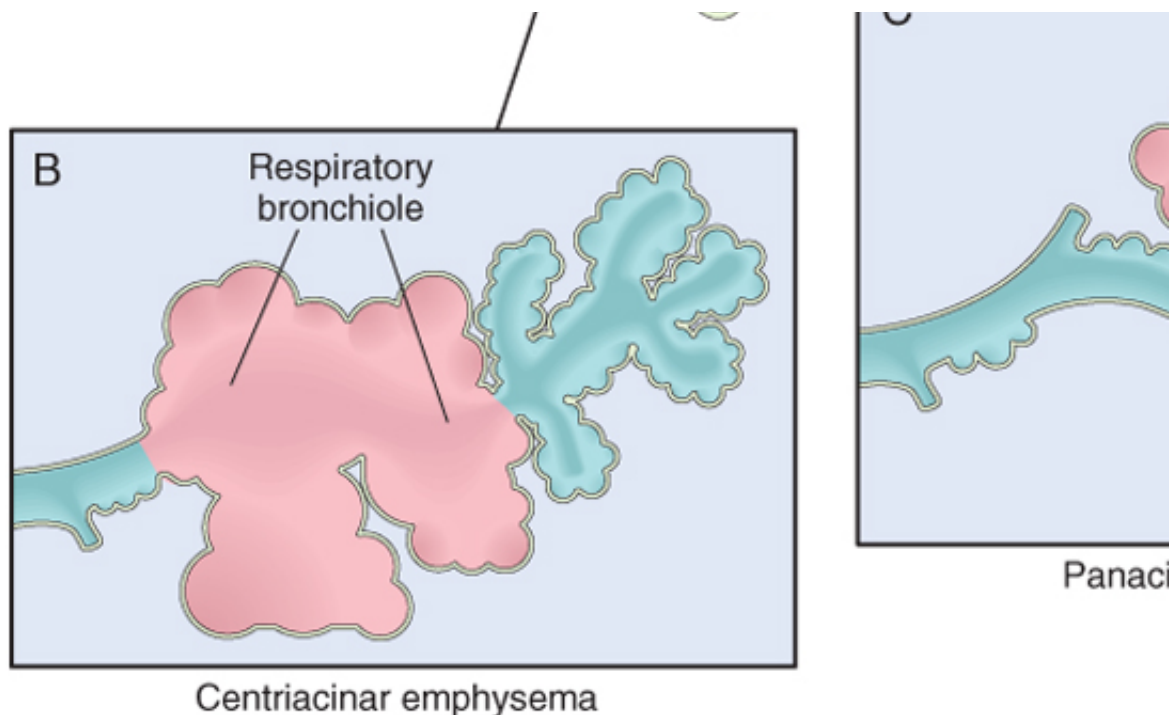
#### Panacinar (Panlobular) Emphysema

In this type of emphysema, the acini are uniformly enlarged from the level of the respiratory bronchiole to the level of the alveolar duct (Fig. 13-6C). In contrast to centriacinar emphysema, panacinar emphysema tends to occur more commonly in people who have congenital deficiency of  $\alpha_1$ -antitrypsin.

#### Distal Acinar (Paraseptal) Emphysema







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 Figure 13-6 **A**, Diagram of normal structures within the acinus, the fundamental unit of the lung. A terminal bronch respiratory bronchiole. **B**, Centrilobular emphysema with dilation that initially affects the respiratory bronchioles. **C** the peripheral structures (i.e., the alveolus and alveolar duct); the disease later extends to affect

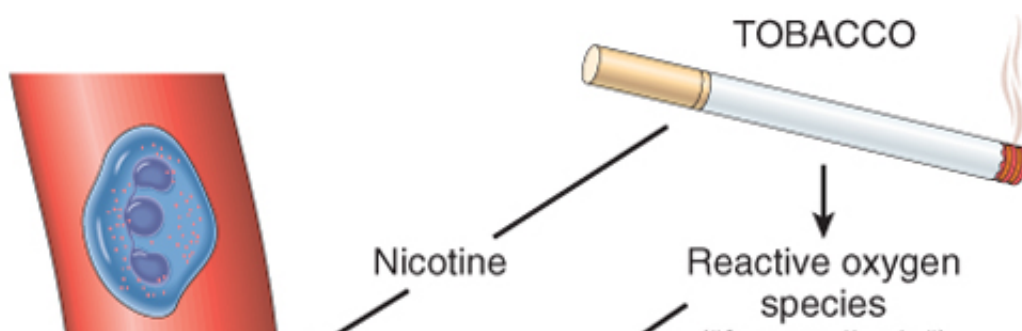
In this form, the proximal portion of the acinus is normal but the distal part is primarily involved. The disease extends to the pleura, along the lobular connective tissue septa, and at the margins of the lobules. It occurs with atelectasis and is usually more severe in the upper half of the lungs. The characteristic findings are enlarged airspaces that range in diameter from less than 0.5 mm to more than 2.0 cm, sometimes progressive enlargement are referred to as *bullae*. This type of emphysema probably underlies many cases of spontaneous pneumothorax in young adults.

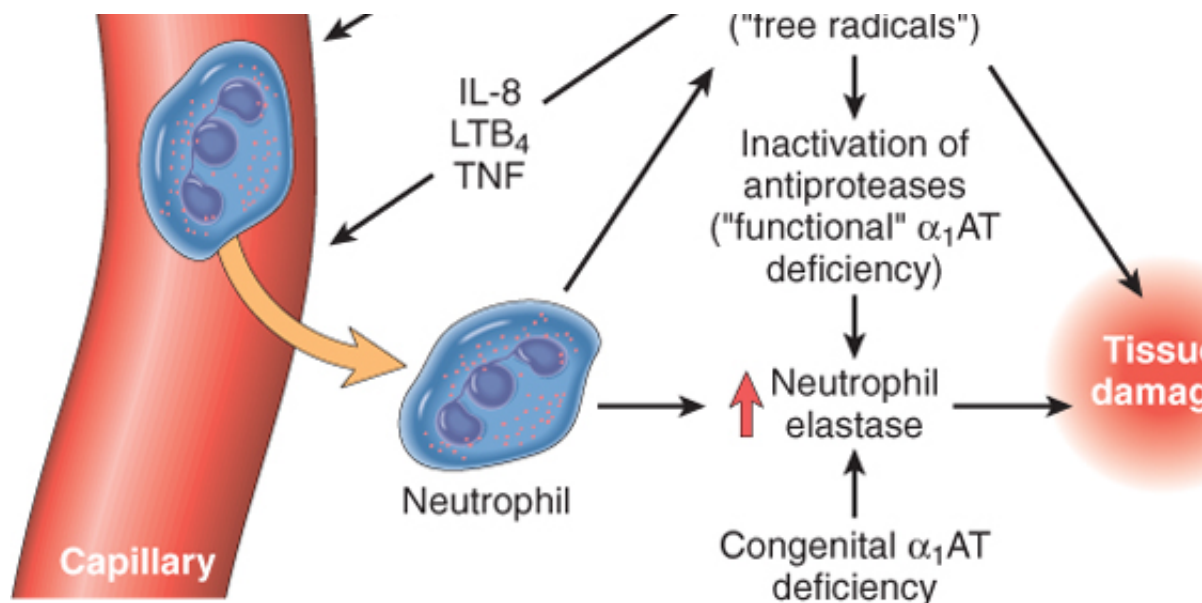
#### Irregular Emphysema

*Irregular emphysema*, so named because the acinus is irregularly involved, is almost invariably associated with healed inflammatory diseases. Although clinically asymptomatic, this may be the most common form of emphysema.

#### Pathogenesis

The genesis of the two common forms of emphysema, centriacinar and panacinar, is not completely understood. Emphysema arising as a consequence of *two critical imbalances*: the protease-antiprotease imbalance (Fig. 13-7). Such imbalances almost always coexist, and in fact, their effects are additive in producing the disease.





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 Figure 13-7 Pathogenesis of emphysema. The protease-antiprotease imbalance and oxidant-antioxidant imbalance lead to tissue damage.  $\alpha_1$ -Antitrypsin ( $\alpha_1$ AT) deficiency can be either congenital or "functional" as a result of oxidative inactivation of  $\alpha_1$ AT. LTB<sub>4</sub>, leukotriene B<sub>4</sub>; TNF, tumor necrosis factor.

The *protease-antiprotease imbalance* hypothesis is based on the observation that patients with  $\alpha_1$ -antitrypsin deficiency have a markedly enhanced tendency to develop pulmonary emphysema, which is common to all patients with emphysema.  $\alpha_1$ -Antitrypsin, normally present in serum, tissue fluids, and secretions, acts as a natural inhibitor of proteases (particularly elastase) secreted by neutrophils during inflammation.  $\alpha_1$ -Antitrypsin is encoded by the proteinase inhibitor (*PI*) locus on chromosome 14. The *PI* locus is extremely polymorphic, with the normal (*M*) allele and the corresponding phenotype. Approximately 0.012% of the US population is associated with markedly decreased serum levels of  $\alpha_1$ -antitrypsin. More than 80% of these individuals are smokers, which occurs at an earlier age and with greater severity if the individual smokes.

The following sequence is postulated:

1. Neutrophils (the principal source of cellular proteases) are normally sequestered in peripheral blood and a few gain access to the alveolar spaces.
2. Any stimulus that increases either the number of leukocytes (neutrophils and macrophages) or the release of protease-containing granules increases proteolytic activity.
3. With low levels of serum  $\alpha_1$ -antitrypsin, elastic tissue destruction is unchecked and emphysema develops.

Thus, emphysema is seen to result from the destructive effect of high protease activity in subjects with  $\alpha_1$ -antitrypsin deficiency. The protease-antiprotease imbalance hypothesis also helps explain the effect of cigarette smoking in the development of emphysema, particularly the centriacinar form in subjects with normal amounts of  $\alpha_1$ -antitrypsin:

*In smokers, neutrophils and macrophages accumulate in alveoli.* The mechanism of inflammation involves the direct chemoattractant effects of nicotine<sup>®</sup> as well as the effects of reactive oxygen species. These factors activate the transcription factor NF- $\kappa$ B, which switches on genes that encode TNF and chemokines that attract and activate neutrophils. Accumulated neutrophils are activated and release their granules, including proteases (neutrophil elastase, proteinase 3, and cathepsin G), resulting in tissue damage. In macrophages, macrophage elastase is not inhibited by  $\alpha_1$ -antitrypsin and, indeed, can be activated by it. There is increasing evidence that in addition to elastase, matrix metalloproteinases derived from macrophages play a role in tissue destruction.

role in tissue destruction.

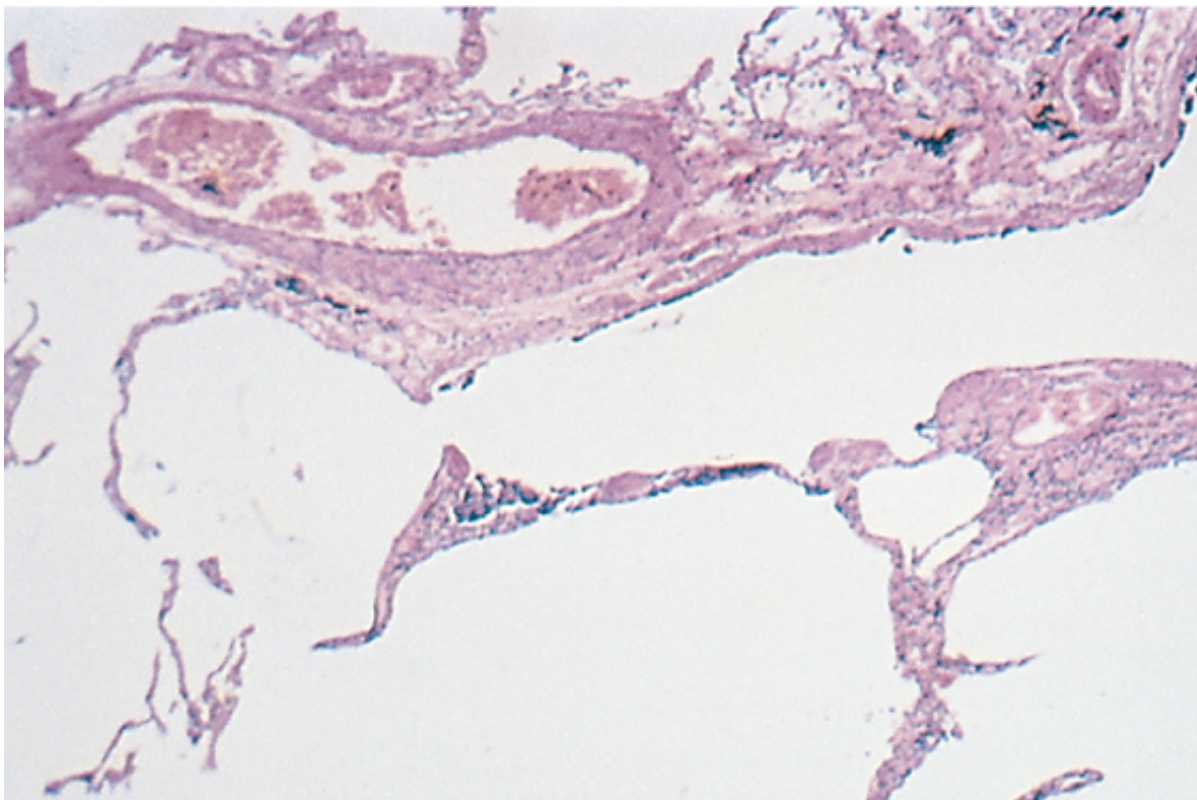
Smoking also has a seminal role in perpetuating the *oxidant-antioxidant imbalance* in the pathogenesis of COPD. The lung contains a healthy complement of antioxidants (superoxide dismutase, glutathione) that keep oxidative damage in check. However, cigarette smoke contains abundant reactive oxygen species (free radicals), which deplete these antioxidants and cause oxidative damage (Chapter 1). Activated neutrophils also add to the pool of reactive oxygen species in the lung. The resulting oxidative injury is inactivation of native antiproteases, resulting in "functional"  $\alpha_1$ -antitrypsin deficiency.

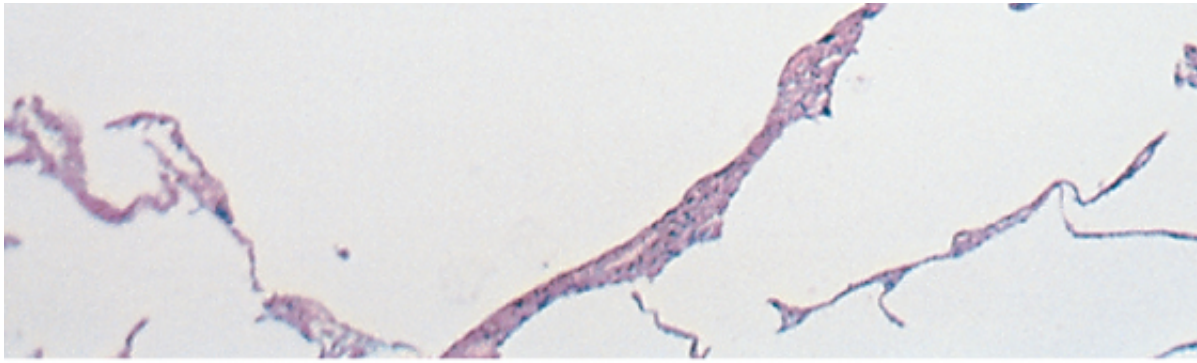
### Morphology

The diagnosis and classification of emphysema depend largely on the macroscopic features. **Panacinar emphysema**, when well developed, produces pale, voluminous lungs that float in water when the anterior chest wall is removed at autopsy. The macroscopic features of **centriacinar emphysema** are less impressive. The lungs are a deeper pink than in panacinar emphysema and the disease is well advanced. Generally, in centriacinar emphysema the upper two-thirds of the lungs are more severely affected than the lower lungs. Histologically there is **thinning and destruction of alveolar septa**. With advanced disease, adjacent alveoli become confluent, creating large airspaces. Respiratory bronchioles may be deformed because of the loss of septa that help maintain their shape. With the **loss of elastic tissue** in the surrounding alveolar septa, there is increased traction on the small airways. As a result, they tend to collapse during expiration-airway obstruction. In addition to alveolar loss, the number of pulmonary capillaries is diminished.

### Clinical Course

**Dyspnea** is usually the first symptom; it begins insidiously but is steadily progressive. In patients with chronic asthmatic bronchitis, cough and wheezing may be initial complaints. Weight loss is common in advanced disease. Pulmonary function tests reveal reduced FEV<sub>1</sub> with normal or near-normal static lung volumes. A hidden malignant tumor may be present.





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 Figure 13-8 Pulmonary emphysema. There is marked enlargement of airspaces, with thinning and destruction of al  
 Department of Pathology, University of Texas Southwestern Medical School, D

The classic presentation in individuals who have no "bronchitic" component is one in which the pa obviously prolonged expiration, sitting forward in a hunched-over position, attempting to squeeze expiratory effort. In these patients, airspace enlargement is severe and diffusing capacity is low. C prominent, so that until very late in the disease, gas exchange is adequate and blood gas values ; prominent dyspnea and adequate oxygenation of hemoglobin, these patients are sometimes calle

On the other extreme are patients with emphysema who also have pronounced chronic bronchitis purulent sputum. They usually have less prominent dyspnea and respiratory drive, so they retain ( often cyanotic. For reasons not entirely clear, they tend to be obese. Often they seek medical help Chapter 11) and associated edema. Patients with this clinical picture are sometimes called "*blue l*

Most individuals with emphysema and COPD fall somewhere between these two classic extremes: *hypertension develops gradually*, arising from both hypoxia-induced pulmonary vascular spasm and area from alveolar destruction. Death from emphysema is related to either pulmonary failure with or right-sided heart failure (cor pulmonale).

## SUMMARY

**Emphysema** Emphysema is a chronic obstructive airway disease character enlargement of airspaces distal to terminal bronchioles. Subtypes include ce smoking related), panacinar (seen in  $\alpha_1$ -antitrypsin deficiency), distal acinar pathogenic mechanisms are an excess of cellular proteases with low antipr antiprotease imbalance), and an excess of reactive oxygen species (oxidan The accumulated inflammatory cells are the source of proteases and oxidar tissue injury and inactivate antiproteases. Most individuals with emphysema chronic bronchitis concurrently, since cigarette smoking is an underlying risk individuals with pure emphysema are characterized as "*pink puffers*."

### Conditions Related to Emphysema

Several conditions resemble emphysema only superficially and are inappropriately referred to as :

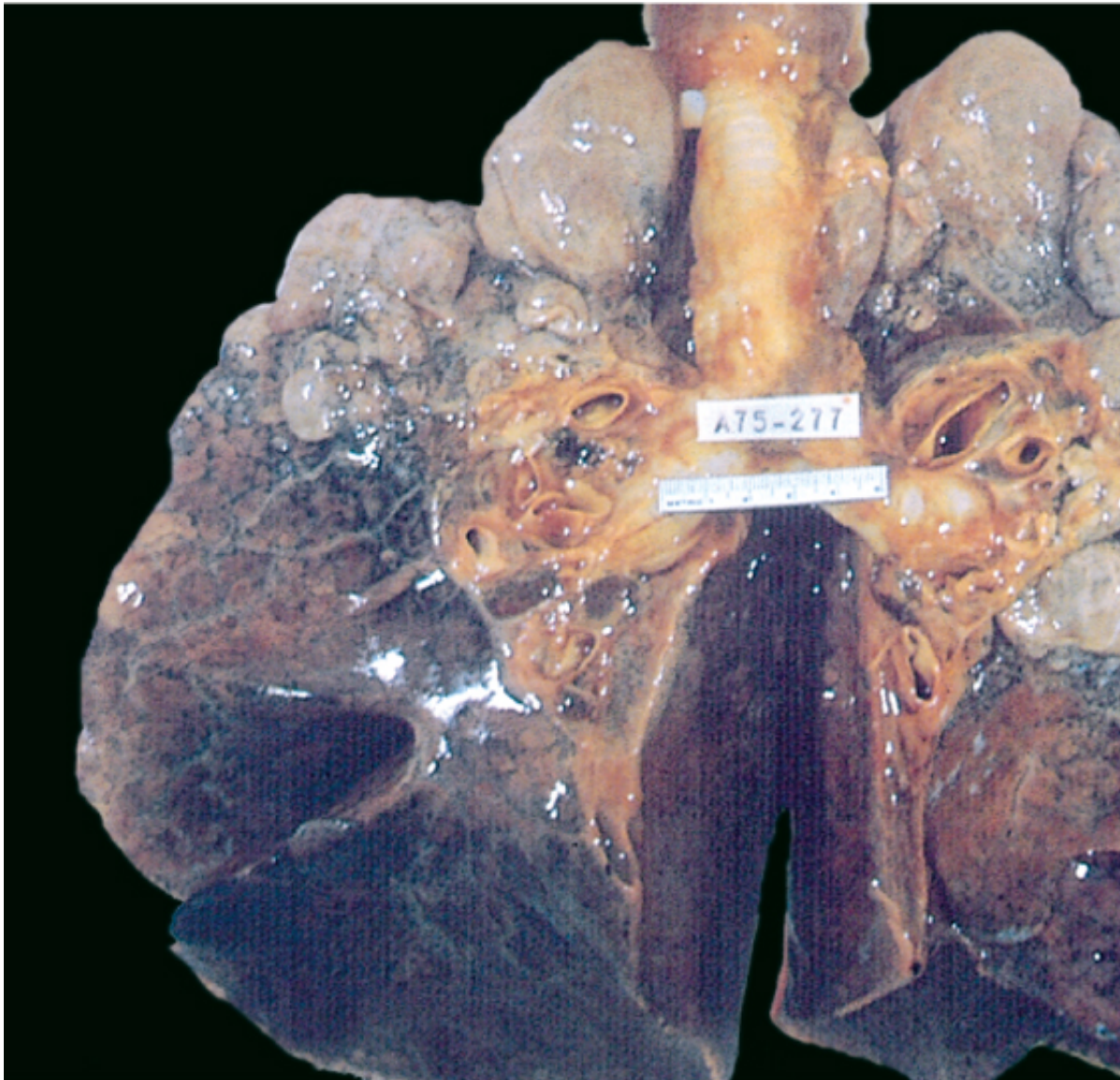
*Compensatory emphysema* is a term used to designate the compensatory dilation of alveoli in res elsewhere, such as occurs in residual lung parenchyma after surgical removal of a diseased lung

*Obstructive overinflation* refers to the condition in which the lung expands because air is trapped \ obstruction by a tumor or foreign object. Obstructive overinflation can be a life-threatening emerge sufficiently to compress the remaining normal lung.

*Bullous emphysema* refers merely to any form of emphysema that produces large subpleural bleb



...emphysema refers merely to any form of emphysema that produces large spaces in the distended state) (Fig. 13-9). They represent localized accentuations of one of the four forms of emphysema and on occasion, rupture leading to pneumothorax.



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Figure 13-9 Bullous emphysema with large apical and subpleural bullae. (From the teaching collection of the University of Texas Southwestern Medical School, Dallas, Texas.)

*Mediastinal (interstitial) emphysema* designates the entrance of air into the connective tissue spaces of the mediastinum or subcutaneous tissue. This may occur spontaneously with a sudden increase in intra-alveolar pressure (e.g., coughing) that causes a tear, with dissection of air into the interstitium. Sometimes it occurs in children, particularly likely to occur in patients on respirators who have partial bronchiolar obstruction or in patients with a rib fracture (e.g., a fractured rib). When the interstitial air enters the subcutaneous tissue, the patient may literally swell of the head and neck and crackling crepitation all over the chest. In most instances, the site of entry is sealed.

### Chronic Bronchitis

Chronic bronchitis is common among cigarette smokers and urban dwellers in smog-ridden cities; recent age group indicate that 20% to 25% have the disease. The diagnosis of chronic bronchitis is

*a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years. It*

Most patients have *simple chronic bronchitis*: the productive cough raises mucoid sputum, patients with chronic bronchitis may demonstrate hyper-responsive airways with intermittent condition referred to as *chronic asthmatic bronchitis*. A subpopulation of bronchitic patients, chronic outflow obstruction, usually with evidence of associated emphysema, and these in *obstructive bronchitis*.

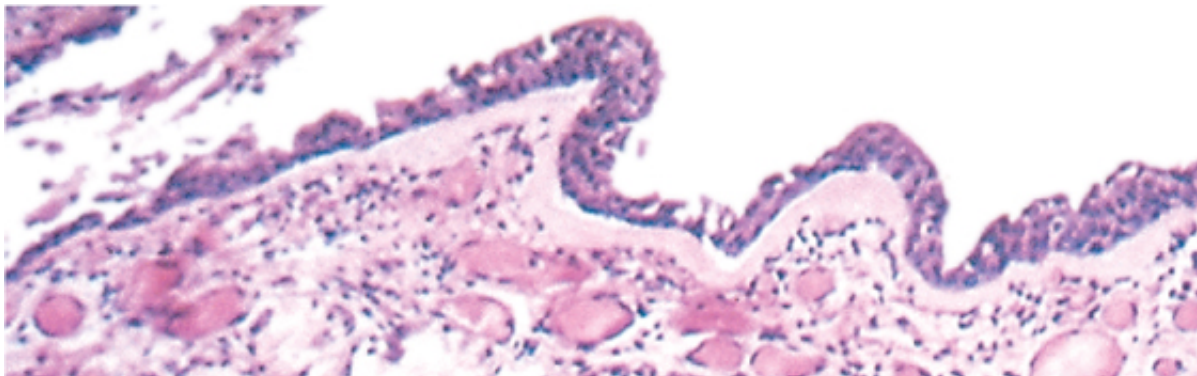
### *Pathogenesis*

The distinctive feature of chronic bronchitis is *hypersecretion of mucus*, beginning in the large airway cause is cigarette smoking, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may induce hypertrophy of mucous glands in the trachea and main-stem bronchi and lead to a marked thickening in the surface epithelium of smaller bronchi and bronchioles. In addition, these irritants cause inflammation with infiltration of macrophages, and neutrophils. In contrast to asthma, eosinophils are lacking in chronic bronchitis. Whereas the defining feature of chronic bronchitis (mucus hypersecretion) is primarily a mucosal involvement, *the morphologic basis of airflow obstruction in chronic bronchitis is more peripheral and involves the small airway disease,* induced by goblet cell metaplasia with mucus plugging of the bronchiolar lumen, peribronchiolar fibrosis, and (2) *coexistent emphysema*. It is generally believed that while small airway disease (an important component of early and relatively mild airflow obstruction, chronic bronchitis with significant airflow obstruction is complicated by emphysema. It is postulated that many of the respiratory epithelial effects of environmental irritants (including mucus hypersecretion) are mediated by local release of T cell cytokines such as IL-13. The transcription factor *MUC5AC*, which is increased as a consequence of exposure to tobacco smoke in both irritant-induced and cigarette-induced bronchitis, is in part mediated by signaling via the epidermal growth factor receptor pathways. *Microbial infectious agents* play a role, chiefly by maintaining the inflammation and exacerbating symptoms.

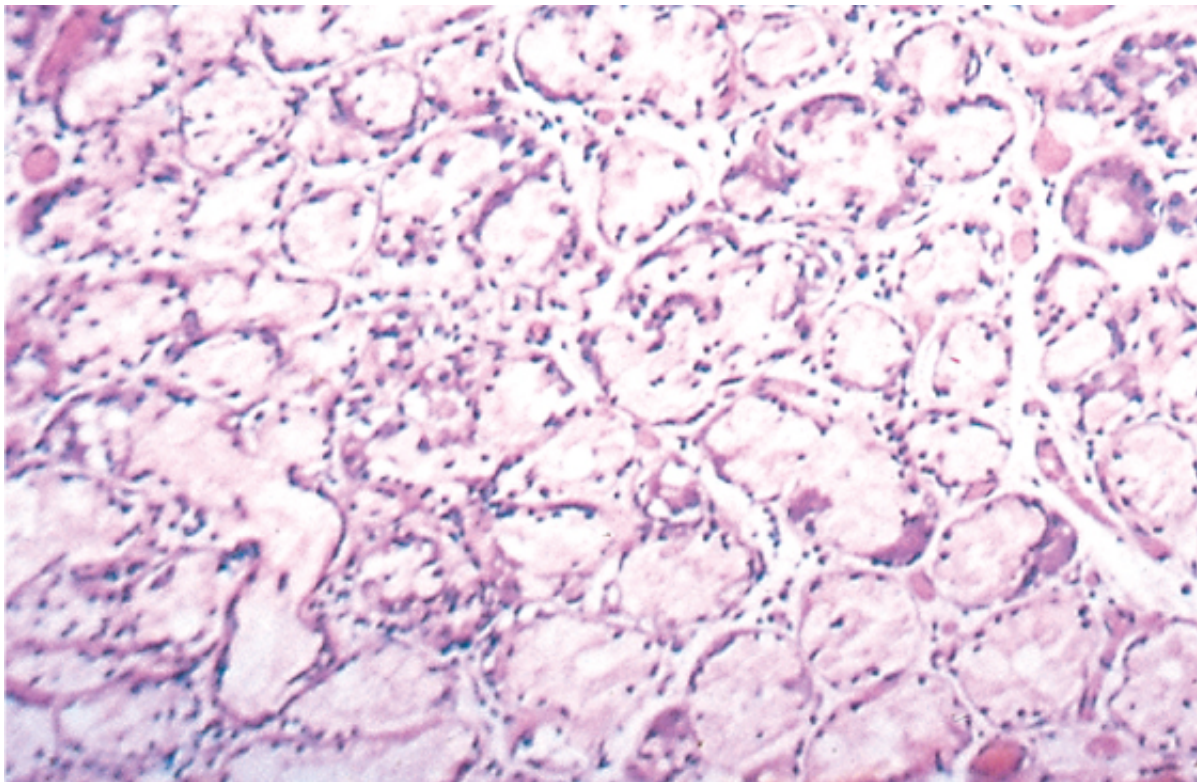
### **Morphology**

Grossly, the mucosal lining of the larger airways is usually **hyperemic and swollen** and is often covered by a layer of mucinous or mucopurulent **secretions**. The smaller bronchi and bronchioles may also be filled with similar secretions. Histologically, the diagnostic feature of chronic bronchitis in the larger bronchi is **enlargement of the mucus-secreting glands** (Fig. 13-10). The degree of enlargement in size is assessed by the ratio of the thickness of the submucosal gland layer to the thickness of the overlying epithelium (Reid index; normally 0.4). A variable density of inflammatory cells, largely mononuclear cells admixed with neutrophils, is frequently present in the bronchial mucosa. The tissue changes are most marked during bronchitic exacerbations, and some studies have shown a relationship between the density of neutrophilic infiltrate and severity of disease. **Chronic bronchiolitis** (small airway disease) is characterized by goblet cell metaplasia, mucus plugging, inflammation, and fibrosis, is also present in chronic bronchitis. In some cases, there may be complete obliteration of the lumen due to fibrosis (bronchiolitis obliterans). As previously stated, it is the peribronchiolar fibrosis and luminal narrowing that result in airflow obstruction.

### *Clinical Course*







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Figure 13-10 Chronic bronchitis. The lumen of the bronchus is above. Note the marked thickening of the mucosa and squamous metaplasia of lung epithelium. (From the teaching collection of the Department of Pathology, University of Texas.)

In individuals with chronic bronchitis, a prominent cough and the production of sputum may persist for years. However, as alluded to earlier, some sufferers develop significant COPD with outflow obstruction, hypercapnia, hypoxemia, and (in severe cases) cyanosis ("*blue bloaters*"). Differentiation of this from emphysema can be made in the classic case ("*pink puffers*," see above), but, as mentioned, many times in the progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure (Chronic heart failure). Respiratory failure are constant threats.

## SUMMARY

**Chronic Bronchitis** Chronic bronchitis is defined as persistent productive cough for at least 3 consecutive months in at least 2 consecutive years. Cigarette smoking is the major underlying risk factor; air pollutants also contribute. Chronic obstructive pulmonary disease (COPD) is a combination of small airway disease (chronic bronchiolitis) and coexistent emphysema. Histologic changes include enlargement of mucus-secreting glands, goblet cell metaplasia, and bronchial wall thickening.

## Asthma

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, cough, and shortness of breath, particularly at night and/or early in the morning. This clinical picture is caused by repeated inflammatory phase reactions in the lung that give rise to the *triad of intermittent and reversible airway obstruction, eosinophils, and bronchial smooth muscle cell hypertrophy and hyperreactivity*. It is thought that increased airway responsiveness (bronchospasm) to a variety of stimuli, which would cause no ill effects in the normal lung, is the key feature. The underlying genetic basis for hyper-responsive airways is not entirely clear, although significant progress has been made in understanding the pathogenesis and environmental triggers of asthma "attack." In some cases, the specific allergen to which the person has been previously sensitized, but often no trigger can be identified. There has been a marked increase in the incidence of asthma in the Western world over the past 3 decades.

Because asthma is a heterogeneous disease triggered by a variety of inciting agents, there is no simple scheme. About 70% of cases are said to be "extrinsic" or "atopic" and are due to IgE and T<sub>H</sub>2-mediated environmental antigens. In the remaining 30% of patients, asthma is said to be "intrinsic" or "non-atopic," with stimuli such as aspirin; pulmonary infections, especially those caused by viruses; cold; psychological stress; and occupational agents. While this distinction is useful from the point of pathophysiology, in clinical practice it is not always

### Pathogenesis

The major etiologic factors of asthma are genetic predisposition to type I hypersensitivity ("atopy") and bronchial hyper-responsiveness to a variety of stimuli. *The inflammation involves many cell types and mediators, but the role of type 2 helper T (T<sub>H</sub>2) cells may be critical to the pathogenesis of asthma.* Associated with an excessive T<sub>H</sub>2 reaction against environmental antigens. Cytokines produced by T<sub>H</sub>2 cells are features of asthma—IL-4 stimulates IgE production, IL-5 activates eosinophils, and IL-13 stimulates epithelial cells to produce chemokines. In addition, epithelial cells are activated to produce chemokines that attract eosinophils, as well as other leukocytes, thus amplifying the inflammatory reaction. In asthma mediated by T<sub>H</sub>2 type cells, asthma is characterized by structural changes in the bronchial wall, remodeling changes include hypertrophy of bronchial smooth muscle and deposition of subepithelial collagen. Remodeling is considered a late, secondary change of asthma; the current view suggests that it may occur over years. The etiologic basis for remodeling is not clear, although there may be an *inherited predisposition*. Polymorphisms in genes that result in accelerated proliferation of bronchial smooth muscle cells have emerged in recent years is *ADAM33*, which is expressed by the cell types implicated in airway remodeling (smooth muscle cells, fibroblasts), although there are undoubtedly other genetic factors involved in this process. *Mast cells* in asthma, are also thought to contribute to airway remodeling by secreting growth factors that stimulate

### Atopic asthma

This most common type of asthma usually begins in childhood. A positive family history of atopy is often preceded by allergic rhinitis, urticaria, or eczema. The disease is triggered by environmental allergens, such as pollen, dust, and foods, but potentially any antigen is implicated. A skin test with the offending antigen elicits a positive reaction, a classic example of the *type I IgE-mediated hypersensitivity reaction* (Chapter 5). In the atopic asthma, the inhaled inciting antigens, which stimulates induction of T<sub>H</sub>2-type cells and release of interleukins, leading to synthesis of IgE that binds to mucosal mast cells. Subsequent IgE-mediated reaction to inhaled allergens causes a *late-phase reaction* (Fig. 13-11B). Exposure of *IgE-coated mast cells* to the same antigen causes release of chemical mediators. Mast cells on the respiratory mucosal surface are initially activated; the release of mediators disrupts intercellular junctions, allowing penetration of the antigen to more numerous mucosal mast cells. *Subepithelial vagal (parasympathetic) receptors* provokes reflex bronchoconstriction through both direct and indirect pathways within minutes after stimulation and is therefore called the *acute, or immediate, response*, which causes bronchoconstriction (due to increased vascular permeability), and mucus secretion. A variety of inflammatory mediators are released during the late-phase response, although their relative importance in an actual asthma attack varies widely. Never

*Leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>*: extremely potent mediators that cause prolonged bronchoconstriction and increase mucin secretion. *Acetylcholine*: released from intrapulmonary motor nerves, causes bronchoconstriction by direct stimulation of muscarinic receptors. *Histamine*: causes bronchospasm but is not considered an important mediator since antihistamine drugs do not provide benefit. *Prostaglandins*: cause bronchoconstriction and vasodilatation. *Platelet-activating factor*: causes aggregation of platelets and release of mediators.

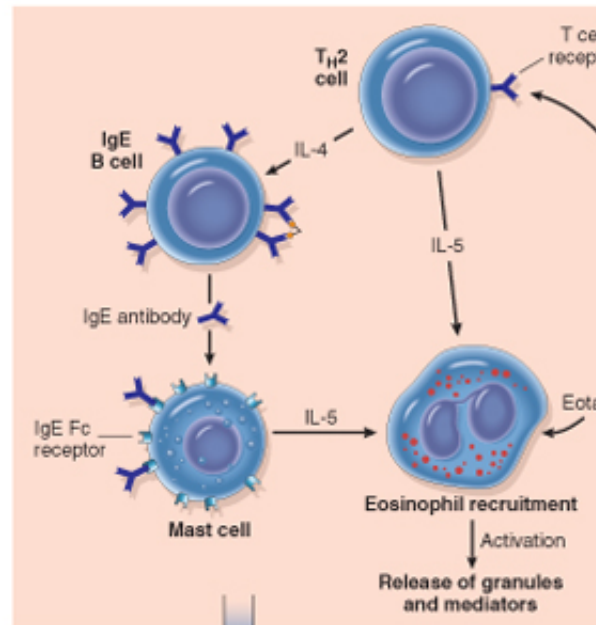
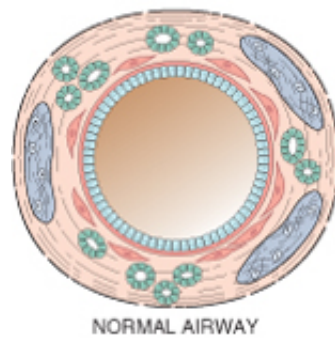
Mast cells also release additional cytokines that cause the influx of other leukocytes, including neutrophils and particularly *eosinophils*. These inflammatory cells set the stage for the *late-phase reaction*, which lasts for 12 to 24 hours, or more (Fig. 13-11C). *Eosinophils* are particularly important in the late phase. The late phase of allergic inflammation is favored by several mast cell-derived chemotactic factors, as well as chemokines released by activated bronchial epithelial cells themselves. The accumulated eosinophils exert a variety of effects as extensive as that of mast cells and includes *major basic protein* and *eosinophil cationic protein*.



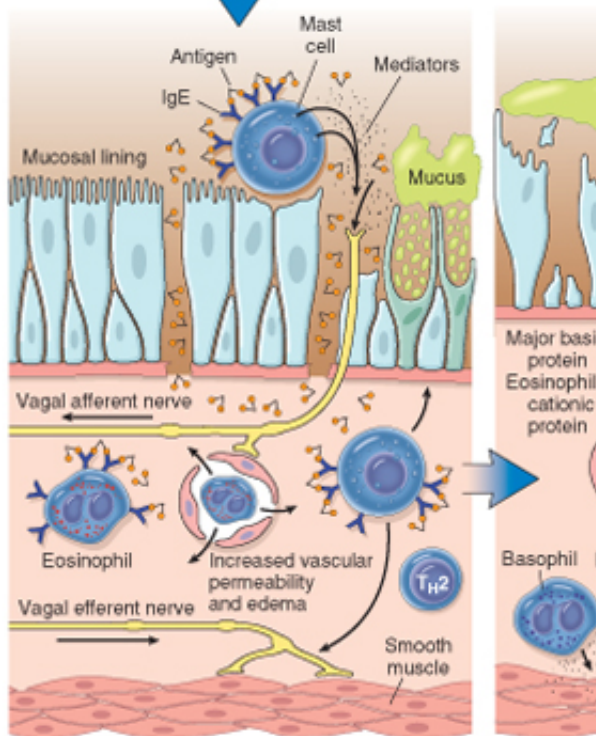
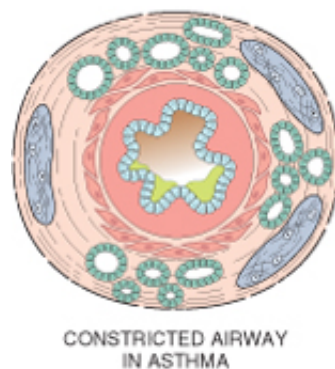
epithelial cells. *Eosinophil peroxidase* causes tissue damage through oxidative stress. Activated e leukotrienes, especially leukotriene C<sub>4</sub>, which contribute to bronchoconstriction. Thus, *eosinophils inflammatory response* without additional exposure to the triggering antigen. The appreciation of t mediators in asthma has led to greater emphasis on anti-inflammatory therapeutics in clinical prac

### Non-Atopic Asthma

#### A. SENSITIZATION TO ALLERGEN



#### B. ALLERGEN-TRIGGERED ASTHMA



IMMEDIATE PHASE (MINUTES)

C. L

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Figure 13.11 A model for allergic asthma. A Sensitization to allergen. Inhaled allergens (antigens) elicit a T<sub>H</sub>2-dr

Figure 13-11 A model for allergic asthma. **A**, Sensitization to allergen. Inhaled allergens (antigens) elicit a  $\text{Type-1}$  eosinophil recruitment (priming or sensitization). **B**, Allergen-triggered asthma. On re-exposure to antigen (Ag) the cross-linking of IgE bound to IgE receptors on mast cells in the airways. These cells release preformed mediators. Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils, which in turn release additional neuronal reflexes, the mediators induce bronchospasm, increased vascular permeability, and mucus production, cells from the blood. **C**, Late phase (hours). The arrival of recruited leukocytes (neutrophils, eosinophils, basophil: phase of asthma and a fresh round of mediator release from leukocytes, endothelium, and epithelial cells. Factors protein, eosinophil cationic protein), also cause damage to the epithel

The mechanism of bronchial inflammation and hyper-responsiveness is much less clear in individuals in such cases are *viral infections of the respiratory tract* (most common) and *inhaled air pollutants* nitrogen dioxide. These agents increase airway hyper-reactivity in both normal and asthmatic subjects. The response, manifested as spasm, is much more severe and sustained. A positive family history is common and there are no associated allergies. *It is thought that virus-induced inflammation of the respiratory subepithelial vagal receptors to irritants.* Although the connections are not well understood, the ultimate airway obstruction (e.g., eosinophils) are common to both atopic and non-atopic variants of asthma.

### Drug-Induced Asthma

Several pharmacologic agents provoke asthma, *aspirin*<sup>®</sup> being the most striking example. Individuals with recurrent rhinitis and nasal polyps, urticaria, and bronchospasm. The precise mechanism remains unclear. *Aspirin*<sup>®</sup> inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxigenase balance toward bronchoconstrictor leukotrienes.

### Occupational Asthma

This form of asthma is stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (various) and other chemicals. Asthma attacks usually develop after repeated exposure to the inciting antigen.

### Morphology

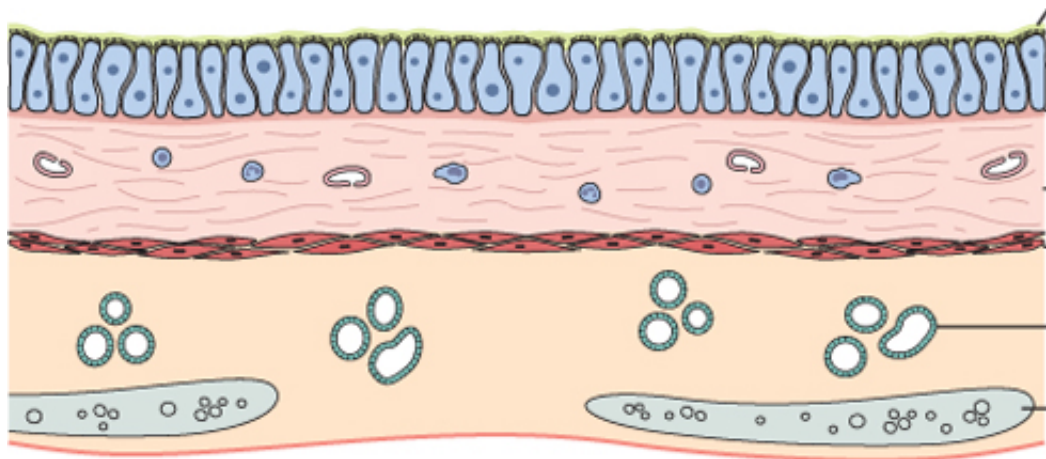
The morphologic changes in asthma have been described in persons who die of pneumonia (status asthmaticus) and in mucosal biopsy specimens of persons challenged with allergen. Grossly, the lungs are overdistended because of overinflation, and there may be secretions in the bronchi. The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick mucus **plugs**. Histologically, the mucus plugs contain whorls of shed epithelium (**Curschmann spirals**), eosinophils and **Charcot-Leyden crystals** (collections of crystalloids made up of eosinophil granules) are also present. The other characteristic findings of asthma, collectively called "airway changes" (Figure 13-12):

Thickening of the basement membrane of the bronchial epithelium. Edema and inflammatory cell infiltrate in the bronchial walls, with a prominence of eosinophils and mast cells. Hypertrophy of the submucosal glands. Hypertrophy of the bronchial muscle walls.

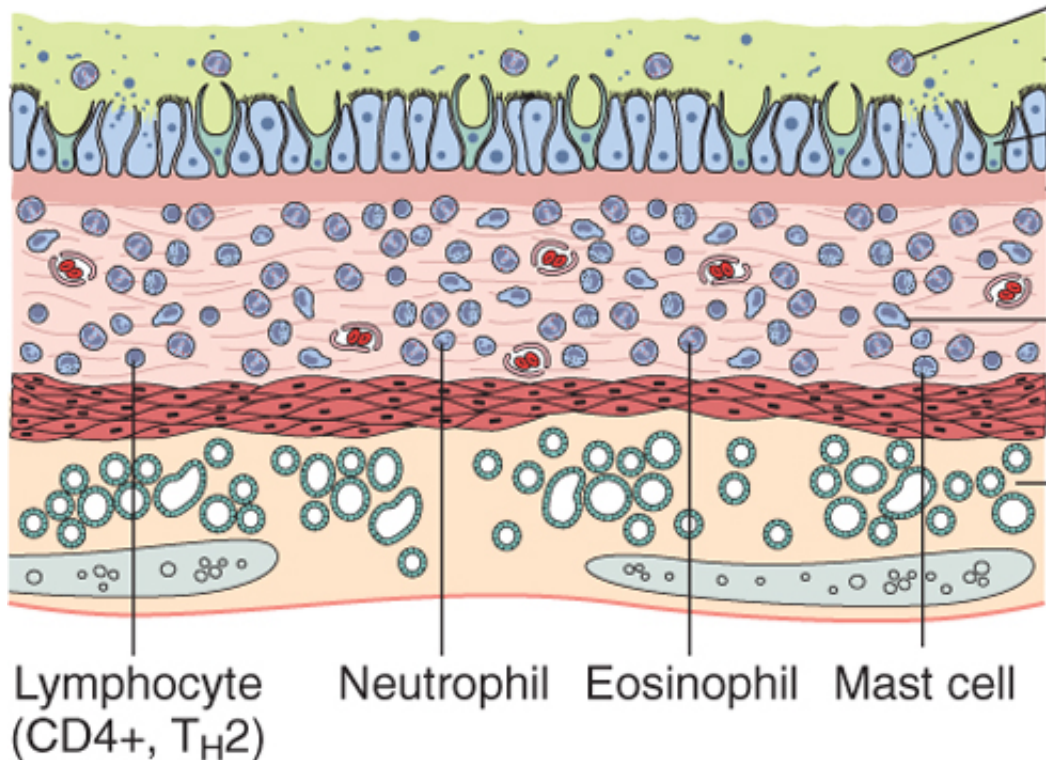
### Clinical Course

An attack of asthma is characterized by severe dyspnea with wheezing; the chief difficulty lies in getting air into the lungs and then cannot get it out, so that there is progressive hyperinflation of the lungs with air trapped in the lungs. The bronchi are constricted and filled with mucus and debris. In the usual case, attacks last from 1 to several hours and respond to therapy, usually bronchodilators and corticosteroids. Intervals between attacks are characteristically long. In severe persistent, subtle respiratory deficits can be detected by spirometric methods. Occasionally a severe attack may respond to therapy and persists for days and even weeks (*status asthmaticus*). The associated hyperinflation may be fatal, although in most cases the disease is more disabling than lethal.

NORMAL



## BRONCHIAL ASTHMA



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 Figure 13-12 Comparison of a normal bronchiole with that in a person with asthma. Note the accumulation of mucus and increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal mucous glands. Inflammation caused by recruitment of eosinophils, macrophages, T<sub>H</sub>2 cells and other inflammatory cells. Basement membrane is thickened, and there is hypertrophy and hyperplasia of smooth muscle.

### SUMMARY

**Asthma** Asthma is characterized by reversible bronchoconstriction caused by increased responsiveness to a variety of stimuli. Atopic asthma is caused by a T<sub>H</sub>2 and IgE-mediated immunologic reaction to environmental allergens and is characterized by airway hyperresponsiveness and airway inflammation. The T<sub>H</sub>2 cytokines IL-4, IL-5, and IL-13 are important mediators of atopic asthma. The pathogenesis of non-atopic asthma are less clear but include viral infections and inhaled air pollution.

atopic asthma are less clear but include viral infections and inhaled air pollutants. Inflammatory cells found in all subtypes of asthma; eosinophil products such as major basic protein are responsible for airway damage. Airway remodeling (basement membrane thickening, hypertrophy of bronchial smooth muscle) adds to the element of obstructive

## Bronchiectasis

Bronchiectasis is the permanent dilation of bronchi and bronchioles caused by destruction of the wall, resulting from or associated with chronic necrotizing infections. It is not a primary disease but rather a complication of obstruction caused by a variety of conditions. Once developed, it gives rise to a characteristic syndrome of chronic expectoration of copious amounts of purulent sputum. Diagnosis depends on an appropriate history and physical examination and on appropriate histologic and radiographic evidence of bronchial dilation. The conditions that most commonly predispose to bronchiectasis include the

*Bronchial obstruction.* Common causes are tumors, foreign bodies, and occasionally impacted feces. If the bronchiectasis is localized to the obstructed lung segment. Bronchiectasis can also coexist with chronic bronchitis. *Congenital or hereditary conditions.* Only a few are cited:

In cystic fibrosis, widespread severe bronchiectasis results from obstruction and infection by an abnormally viscid mucus. This is an important and serious complication ([Chapter 7](#)). In immunoglobulin deficiencies, bronchiectasis is likely to develop because of an increased susceptibility to infections; localized or diffuse bronchiectasis can occur. Kartagener syndrome, an autosomal recessive disorder associated with bronchiectasis and with sterility in males. Structural abnormalities of the cilia and flagella of the airways, leading to persistent infections, and reduce the mobility of spermatozoa. *Necrotizing, or suppurative, pneumonia*, particularly with virulent organisms such as *Staphylococcus aureus*, predispose to bronchiectasis. In the past, postinfective bronchiectasis was sometimes a sequel to severe measles, whooping cough, and influenza, but this has substantially decreased since the introduction of immunization. Post-tubercular bronchiectasis continues to be a significant cause of morbid

## Pathogenesis

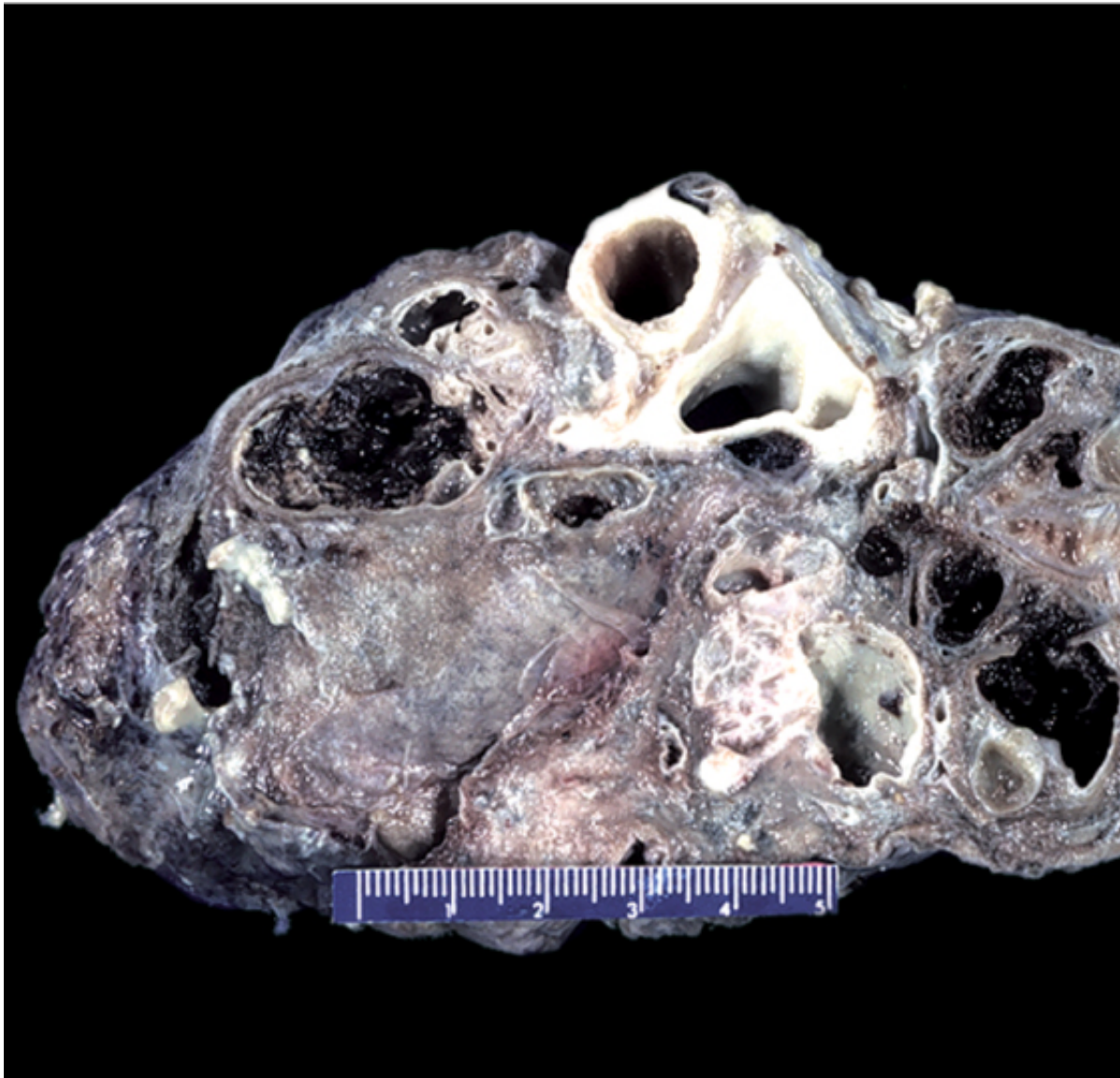
Two processes are crucial and intertwined in the pathogenesis of bronchiectasis: *obstruction and infection*. These two processes may come first. Normal clearance mechanisms are hampered by obstruction; conversely, chronic infection in time causes damage to bronchial walls, leading to weakening and distortion. A bronchogenic carcinoma or a foreign body impairs clearance of secretions, providing a fertile medium for infection and resultant inflammatory damage to the bronchial wall and the accumulating exudate further distends and dilates the bronchus. Conversely, a persistent necrotizing inflammation in the bronchi or bronchioles may cause destruction of the wall (with peribronchial fibrosis and traction on the walls), and eventually the trachea

## Morphology

Bronchiectatic involvement of the lungs usually affects the **lower lobes** bilaterally, particularly the bronchi and bronchioles that are most vertical. When tumors or aspiration of foreign bodies lead to obstruction, involvement may be sharply localized to a single segment of the lungs. Usually, the disease is found in the more distal bronchi and bronchioles. The airways may be **dilated** to 2-3 times their usual diameter and on gross examination of the lung can be followed almost to the periphery ([Fig. 13-13](#)). (By contrast, in normal lungs, the bronchioles cannot be followed by ordinary dissection beyond a point 2-3 cm from the pleural surfaces.) The histologic findings vary with the stage of the disease. In the full-blown active case, an **intense acute and chronic inflammation** of the walls of the bronchi and bronchioles and the desquamation of lining epithelium with areas of ulceration. In the usual case, a **mixed** flora can be cultured from the involved bronchi, including staphylococci, streptococci, pneumococci, enteric organisms, anaerobic and micrococci (particularly in children) *Haemophilus influenzae* and *Pseudomonas aeruginosa*. The lining epithelium may regenerate completely; however, usually so much injury has occurred that dilation and scarring persist. Fibrosis of the bronchial and bronchiolar walls and peribronchovascular thickening develop in more chronic cases. In some instances, the necrosis destroys the bronchus and forms a lung abscess.



### Clinical Course



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Figure 13-13 Bronchiectasis. Cross-section of lung demonstrating dilated bronchi extending almost to the pleura.  
Pathology, University of Texas Southwestern Medical School, Dallas, TX

The clinical manifestations consist of severe, persistent cough with expectoration of mucopurulent sputum that may contain flecks of blood; frank hemoptysis can occur. Symptoms are often episodic and are precipitated by respiratory infections or the introduction of new pathogenic agents. Clubbing of the fingers may develop. In contrast to obstructive pulmonary disease, in bronchiectasis, significant obstructive ventilatory defects develop, with hypoxemia, hypercapnia, and cor pulmonale. Metastatic brain abscesses and reactive amyloidosis (Chapter 5) are other, less frequent complications.



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## DIFFUSE INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES

Diffuse interstitial (restrictive) lung diseases are a heterogeneous group of disorders *characterized by chronic involvement of the pulmonary connective tissue, principally the most peripheral and delicate portions*, the pulmonary interstitium is composed of the basement membrane of the endothelium (the thinnest portions), collagen fibers, elastic tissue, fibroblasts, a few mast cells, and occasional macrophages. Some group are of unknown cause and pathogenesis; some have an intra-alveolar as well as an interstitial component. There is overlap in histologic features among the different conditions. Nevertheless, the presence of similar alterations, and pathophysiologic changes justifies their consideration as a group. Although chest radiographs, mentioned earlier, can also cause restrictive disease, this discussion will concentrate on parenchymal changes. Symptoms of restrictive lung disease can be inferred from the morphologic changes. *The hallmark is decreased compliance* (i.e., more pressure is required to expand the lungs because they are stiff), which in turn causes difficulty breathing (dyspnea). Furthermore, damage to the alveolar epithelium and interstitial vasculature produces a ventilation-perfusion ratio, leading to *hypoxia*. Chest radiographs show diffuse infiltration by small nodules, in the peripheral regions (Fig. 11). With progression, individuals can develop respiratory failure, often in association with pulmonary hypertension (Fig. 11).

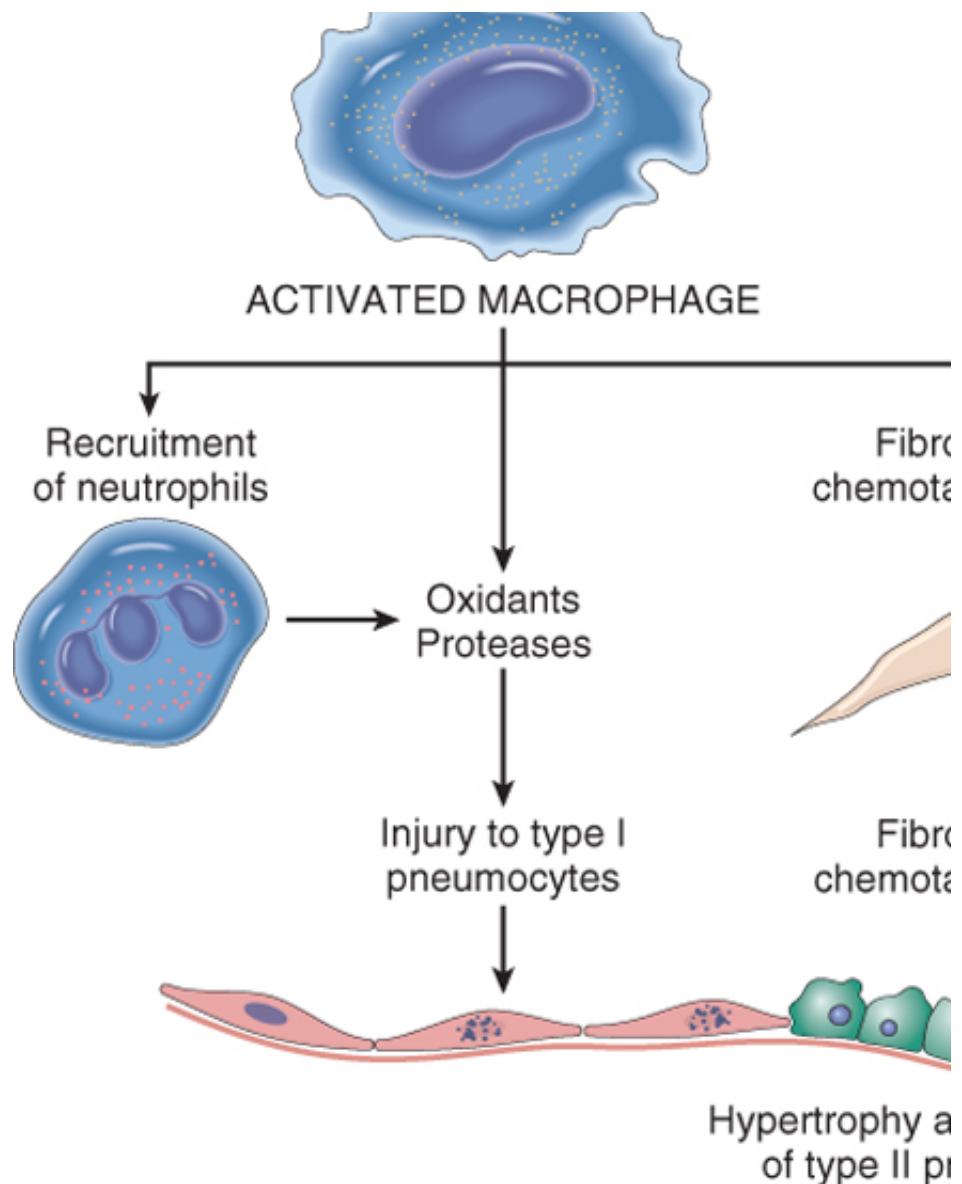
Diffuse infiltrative diseases are categorized either as clinicopathologic syndromes or as having characteristic histologic features. At the end stage of most chronic restrictive lung diseases, irrespective of etiology, is diffuse interstitial fibrosis. *Honeycombing*, there are often sufficient histologic pointers in biopsy material (e.g., the existence of thickened alveolar septa, to narrow, if not pinpoint, the diagnosis. An accurate social and occupational history is indispensable in the diagnosis of the histologic tissue.

### Pathogenesis

**Table 13-3. Major Categories of Chronic Interstitial Lung Disease**

<b>Fibrosing</b>
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Associated with collagen vascular disease
Pneumoconiosis
Associated with therapies (drugs, radiation)
<b>Granulomatous</b>
Sarcoidosis
Hypersensitivity pneumonia
<b>Eosinophilic</b>
<b>Smoking Related</b>
Desquamate interstitial pneumonia
Respiratory bronchiolitis





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Figure 13-14 General scheme for the pathogenesis of chronic restrictive lung disease.

It is now thought that regardless of the type of interstitial disease or specific cause, the earliest common feature in all interstitial diseases is *alveolitis*, that is, accumulation of inflammatory and immune effector cells within the alveolar space. If the injury is mild and self-limited, resolution with restoration of normal architecture follows. However, if the injury is severe and persistent, *cellular interactions involving lymphocytes, macrophages, and neutrophils lead to parenchymal injury and progressive interstitial fibrosis* (Fig. 13-14). Activation of pulmonary macrophages is a key event in the pathogenesis of chronic restrictive lung disease. Activated macrophages secrete chemoattractants (e.g., IL-8 and leukotriene B<sub>4</sub>) that recruit and activate neutrophils. Mediators (oxidants, proteases) released from macrophages and recruited neutrophils injure alveolar cells and the underlying connective tissue. Alveolar macrophages also secrete a host of "fibrogenic" factors, including fibroblast growth factor  $\beta$  (TGF- $\beta$ ), and platelet-derived growth factor, which can attract *fibroblasts* as well as stimulate a repair response. It is now believed that alveolar epithelial cells are not merely passive targets of injury. Injury to type I pneumocytes is often accompanied by proliferation of type II pneumocytes. These cells secrete chemotactic protein 1) that attract additional macrophages to the alveolar milieu. In addition, they secrete platelet-derived growth factor and other fibrogenic cytokines, such as TGF- $\beta$ . Drugs to inhibit TGF-

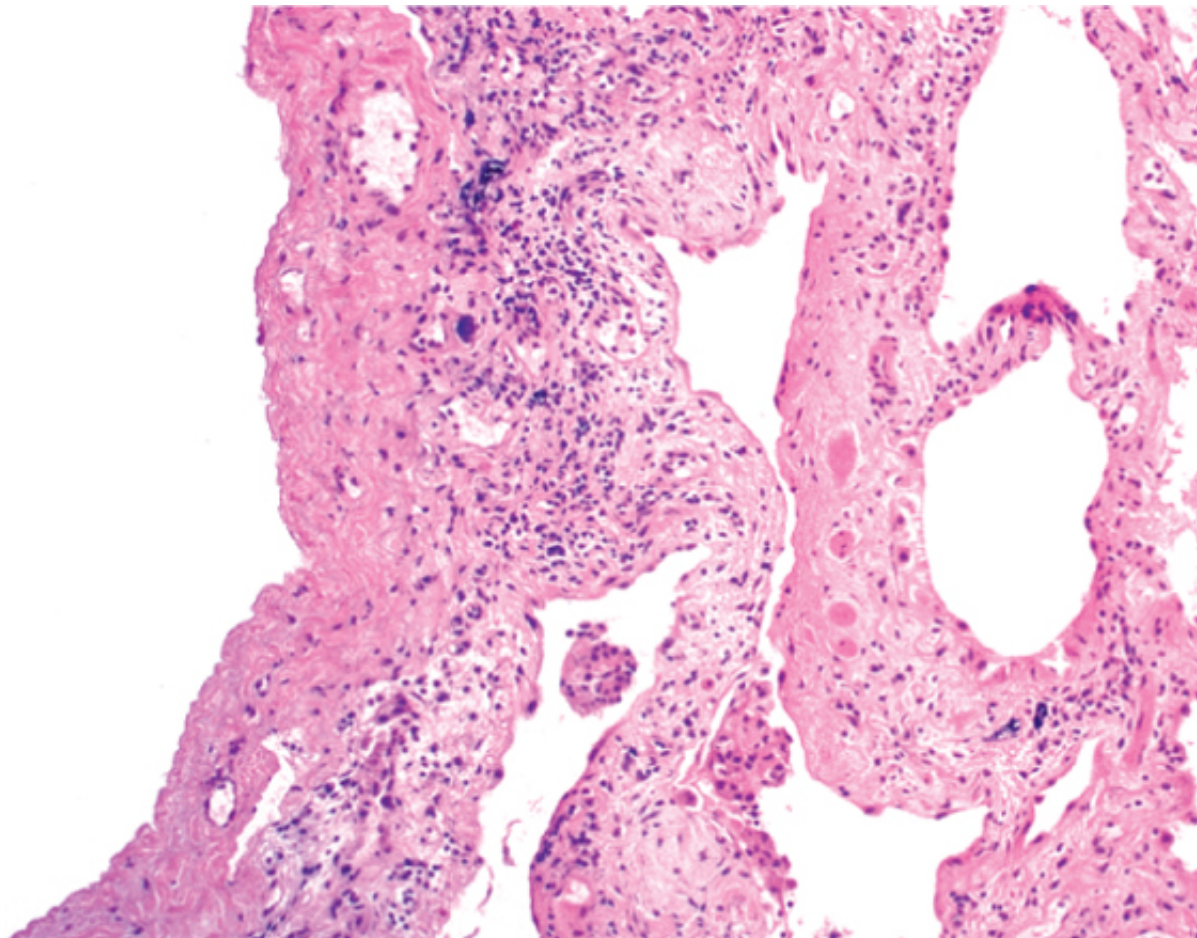
## Fibrosing Diseases

### **Idiopathic Pulmonary Fibrosis**

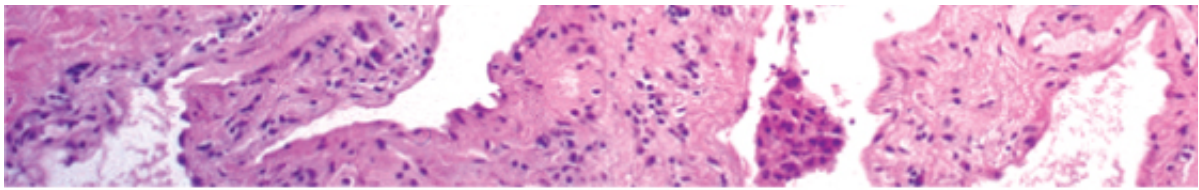
Idiopathic pulmonary fibrosis (IPF), also known as *cryptogenic fibrosing alveolitis*, refers to a pulmonary disease characterized histologically by diffuse interstitial fibrosis, which in advanced cases results in severe architectural distortion. The exact agent for recurrent alveolitis in IPF is unknown. Males are affected more often than are females, and patients are older than 60 years of age at presentation. The histologic pattern of fibrosis is referred to as *usual interstitial pneumonia* (UIP). It should be stressed, however, that similar pathologic findings in entities such as asbestosis, the collagen-vascular diseases, and a number of other conditions. The term "idiopathic" is used.

#### **Morphology**

Grossly, the pleural surfaces of the lung have the appearance of cobblestones because of scars along the interlobular septa. The cut surface shows fibrosis (firm, rubbery) with a predominance and a distinctive distribution in the subpleural regions and along the bronchi. The pattern of fibrosis in IPF is referred to as **usual interstitial pneumonia (UIP)**. The pattern is **patchy interstitial fibrosis**, which varies in intensity (Fig. 13-15) and with time. Early lesions contain exuberant fibroblastic proliferation and appear as **fibroblastic foci** (Fig. 13-15). As time progresses, these areas become more collagenous and less cellular. Quite typical is the existence of **(temporal heterogeneity)**. The dense fibrosis causes collapse of alveolar walls and spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (**honeycombing**). Interstitial inflammation is usually patchy and consists of an alveolar septal infiltrate of lymphocytes and occasional plasma cells, mast cells, and eosinophils. Secondary pulmonary hypertension (intimal fibrosis and medial thickening of pulmonary arteries) are often present.





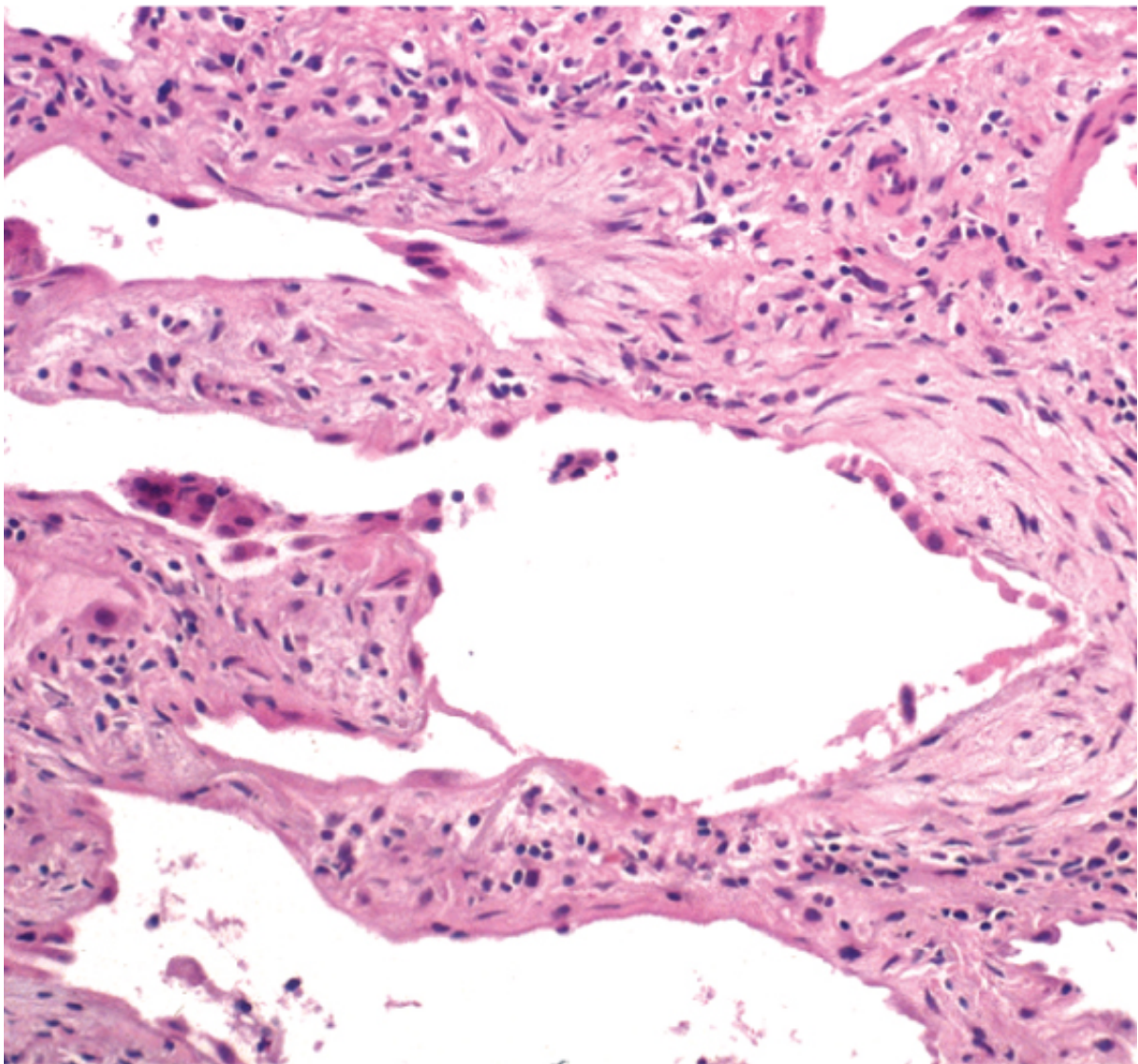


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Figure 13-15 Usual interstitial pneumonia. The fibrosis, which varies in intensity, is more pronou

#### *Clinical Course*

IPF usually presents insidiously, with the gradual onset of a nonproductive cough and progressive individuals with IPF have characteristic "dry" or "Velcro"-like crackles during inspiration. Cyanosis, may develop in the later stages of the disease. Surgical lung biopsy remains the gold standard for causes of pulmonary fibrosis. Unfortunately, the progress of IPF is relentless despite therapy, and Lung transplantation is the only definitive therapy available.

#### ***Nonspecific Interstitial Pneumonia***



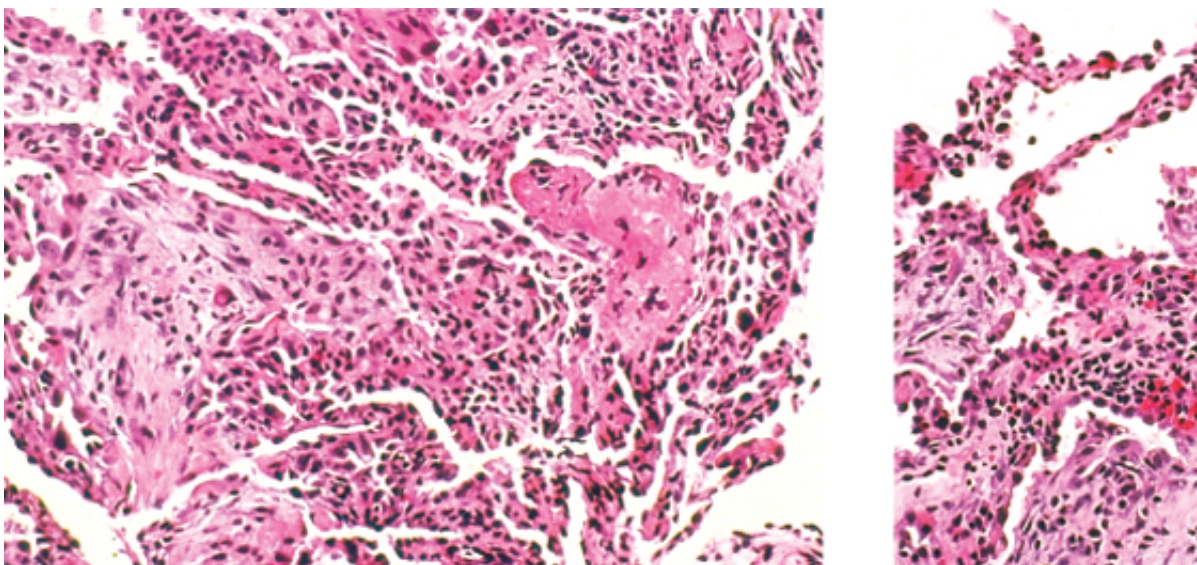
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Figure 13-16 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and

Patients with nonspecific interstitial pneumonia have a diffuse interstitial lung disease of unknown etiology. They show diagnostic features of any of the other well-characterized interstitial diseases. Though it is important to differentiate non-specific interstitial fibrosis from UIP, since the former has a better prognosis. Specific interstitial pneumonia is divided into cellular and fibrosing patterns. The *cellular pattern* is composed of mild-to-moderate chronic interstitial inflammation (lymphocytes and a few plasma cells). The *fibrosing pattern* consists of diffuse or patchy interstitial fibrosis, *without the temporal heterogeneity*; foci are typically absent. Patients present with dyspnea and cough of several months' duration. Patients with the cellular pattern have a better outcome than those with the fibrosing pattern and UIP.

### **Cryptogenic Organizing Pneumonia**

Cryptogenic organizing pneumonia is synonymous with "bronchiolitis obliterans organizing pneumonia" (BOOP), which is preferred, since it emphasizes the unknown etiology of this clinicopathologic entity. Patients present with radiographically have subpleural or peribronchial patchy areas of airspace consolidation. Histology is characterized by the presence of polypoid plugs of loose organizing connective tissue within alveolar bronchioles (Fig. 13-17). The connective tissue is all of the same age, and the underlying lung architecture is preserved. Patients recover spontaneously, but most require treatment with oral steroids for 6 months or longer. Of note, alveolar fibrosis can also be seen as a response to infections (e.g., pneumonia) or inflammatory injury (e.g., transplantation injury) to the lung; in these cases the etiology is obviously not "cryptogenic."

### **Pulmonary Involvement in Collagen Vascular Diseases**



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Figure 13-17 Cryptogenic organizing pneumonia. Alveolar spaces are filled with balls of

Many collagen vascular diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis) are associated with pulmonary manifestations. Several histologic variants can be seen, including NSIP, UIP-pattern (similar to what is seen in IPF), vascular sclerosis, organizing pneumonia, with or without fibrosis) being the most common. Pleural involvement (pleuritis, pleural nodules, and thickening) is also seen. Pulmonary involvement in these diseases is usually associated with a poor prognosis, although it

### **SUMMARY**

**Diffuse Interstitial Fibrosis** Diffuse interstitial fibrosis of the lung gives rise to a restrictive lung disease characterized by reduced lung compliance and reduced forced vital capacity (FVC). The diseases that cause diffuse interstitial fibrosis are heterogeneous, and the pathogenetic factor is injury to the alveoli with activation of macrophages and



cytokines such as TGF- $\beta$ . Idiopathic pulmonary fibrosis, is prototypic of restrictive lung disease, characterized by patchy lung fibrosis and formation of cystic spaces (honeycombing). This pattern is known as *usual interstitial pneumonia*.

## Pneumoconioses

**Table 13-4. Mineral Dust-Induced Lung Disease**

Agent	Disease	Exposure
Coal dust	Simple coal workers' pneumoconiosis: macules and nodules Complicated coal workers' pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarry work, ceramics
Asbestos	Asbestosis pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and installation and removal

PMF, progressive massive fibrosis.

*Pneumoconiosis* is a term originally coined to describe the non-neoplastic lung reaction to inhaled dust, but has been broadened to include diseases induced by organic as well as inorganic particulates, and some exogenous vapor-induced non-neoplastic lung diseases as pneumoconioses. The mineral dust pneumoconioses result from exposure to coal dust, silica, and asbestos—nearly always result from exposure in the workplace. Lung cancer as a result of asbestos exposure extends to family members of asbestos workers and to others outside the workplace. Table 13-4 indicates the pathologic conditions associated with each mineral dust; the dust exposure is sufficient to produce disease.

### Pathogenesis

The reaction of the lung to mineral dusts depends on many variables, including size, shape, solubility, and toxicity. For example, particles greater than 5 to 10  $\mu\text{m}$  are unlikely to reach distal airways, whereas particles smaller than 5  $\mu\text{m}$  move into and out of alveoli, often without substantial deposition and injury. *Particles that are most injurious are those that get lodged at the bifurcation of the distal airways.* Coal dust is relatively inert, and lung disease before lung disease is clinically detectable. Silica, asbestos, and beryllium are more reactive and cause severe reactions at lower concentrations. Most inhaled dust is entrapped in the mucus blanket and rapidly cleared by mucociliary movement. However, some of the particles become impacted at alveolar duct bifurcations, where they are phagocytosed by endocytose the trapped particulates. *The pulmonary alveolar macrophage is a key cellular element in the pathogenesis of injury and fibrosis.* The more reactive particles trigger the macrophages to release a number of proinflammatory mediators in response and initiate fibroblast proliferation and collagen deposition. Some of the inhaled particles are cleared by direct drainage or within migrating macrophages and thereby initiate an immune response to components of the particles that are modified by the particles. This then leads to an amplification and extension of the inflammatory response, which worsens the effects of all inhaled mineral dusts, more so with asbestos than with any other particle.

### Coal Workers' Pneumoconiosis

A number of British novels, including D. H. Lawrence's *Sons and Lovers*, poignantly describe the lives of the twentieth century who toiled underground all their lives, only to die of "black lung" complicated by pneumoconiosis. The fact that the use of mechanical ventilation in coal mines has drastically reduced the incidence of coal dust-induced disease. The spectrum of lung disease ranges from *asymptomatic anthracosis*, in which pigment accumulates without a perceptible cellular response, to *simple coal workers' pneumoconiosis* (CWP), in which accumulations of macrophages occur with little to no pulmonary function impairment, to *progressive massive fibrosis* (PMF), in which fibrosis is extensive and lung function is compromised. Although the spectrum varies, it seems that fewer than 10% of cases of simple CWP progress to PMF. It should be noted that a confluent fibrosing reaction in the lung; this can be a complication of any one of the three pneumoconioses.

Although coal is mainly carbon, coal mine dust contains a variety of trace metals, inorganic minerals, and organic compounds. The ratio of carbon to contaminating chemicals and minerals ("coal rank") increases from bituminous to anthracite, and anthracite has been associated with a higher risk of CWP.

has been associated with a higher risk of CWP.

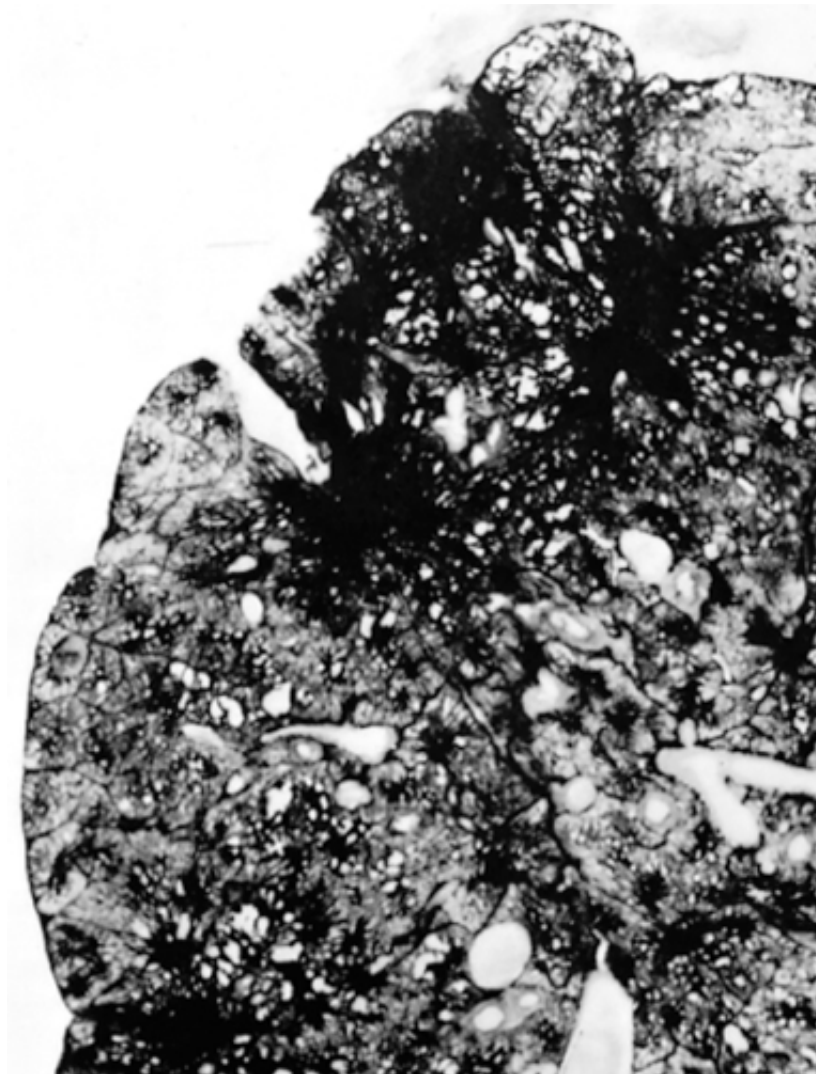
### **Morphology**

**Pulmonary anthracosis** is the most innocuous coal-induced pulmonary lesion in CWP, commonly seen in all urban dwellers and tobacco smokers. Inhaled carbon pigment is phagocytized by interstitial macrophages, which then accumulate in the connective tissue along the pleural lymphatics, or in lymph nodes.

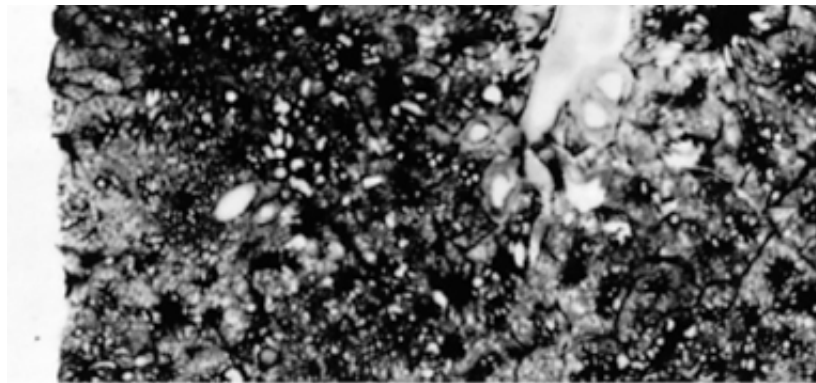
**Simple CWP** is characterized by **coal macules** and the somewhat larger **coal nodules**, which consist of dust-laden macrophages; in addition the nodule contains small amounts of collagen fibers. Although these lesions are scattered throughout the lung, the upper lobes and the lower lobes are more heavily involved. In due course, **centrilobular emphysema** develops. Functionally significant emphysema is more common in the United Kingdom and Europe than in the United States. The coal rank is higher than in the United States.

**Complicated CWP (PMF)** occurs on a background of simple CWP by coalescence of nodules and generally requires many years to develop. It is characterized by intensely blackened areas, sometimes up to 10 cm in greatest diameter. They are usually multiple (Fig. 13-18). The lesions consist of dense collagen and pigment.

### *Clinical Course*







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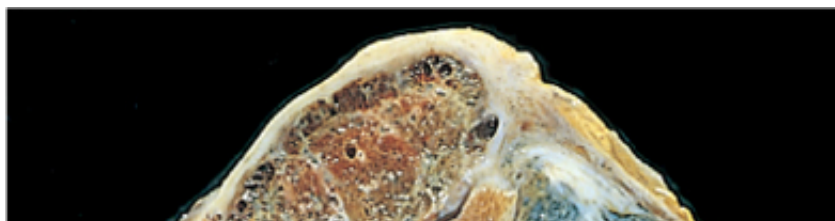
Figure 13-18 Progressive massive fibrosis superimposed on coal workers' pneumoconiosis. The large blackened extensions of scars into surrounding parenchyma and retraction of adjacent pleura. (Courtesy of Dr. Werner Lac Institute of Occupational Safety and Health.)

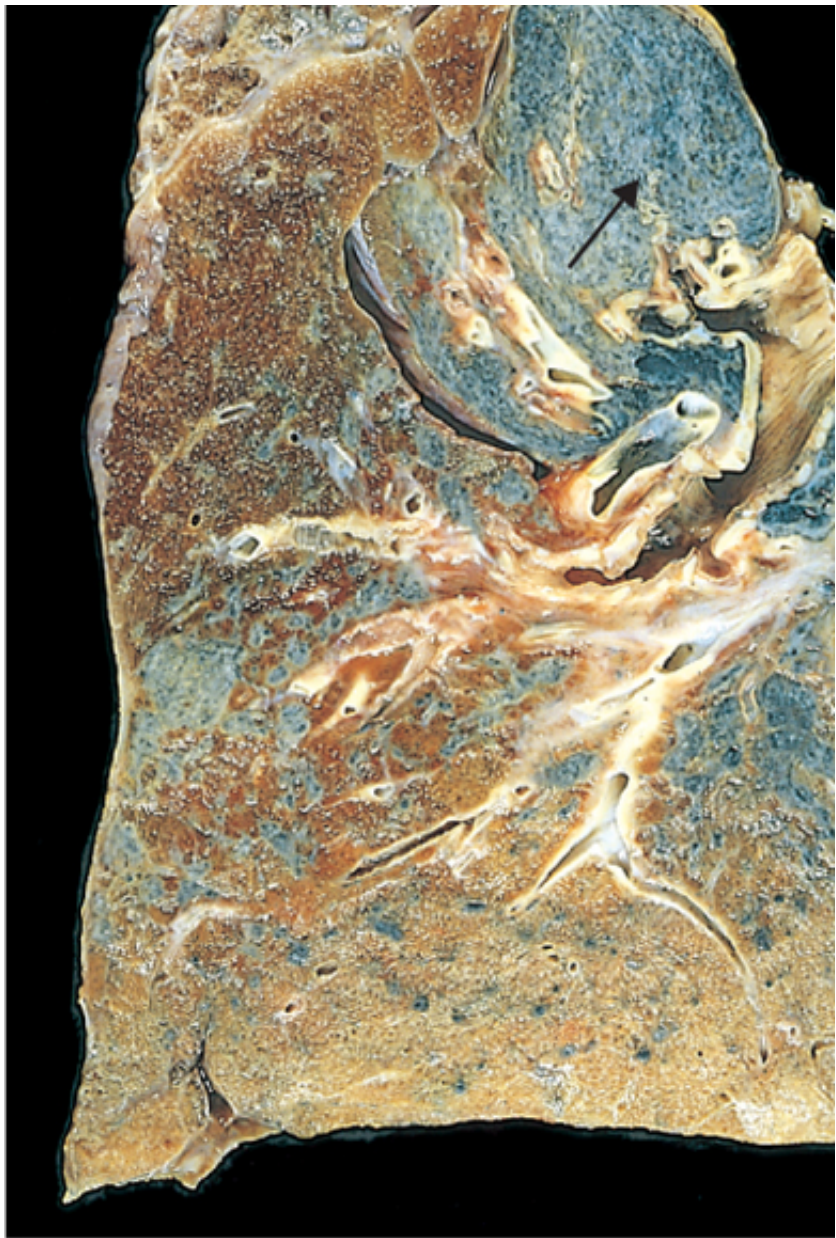
CWP is usually a benign disease that produces little decrement in lung function. In those in whom pulmonary dysfunction, pulmonary hypertension, and cor pulmonale. Progression from CWP to PMF depends on further exposure. Once smoking-related risk has been taken into account, there is no increased risk for coal miners, a feature that distinguishes CWP from both silica and asbestos exposures (see below).

**Silicosis**  
Silicosis is currently the most prevalent chronic occupational disease in the world. It is caused by occupational settings. Silica occurs in both crystalline and amorphous forms, but crystalline forms (tridymite) are by far the most toxic and fibrogenic. Of these, quartz is most commonly implicated in lung disease. Inhaled silica particles cause activation and release of cytokines from macrophages, including IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and others. A compelling piece of evidence incriminating TNF, since anti-TNF monoclonal antibodies can block lung disease when given intratracheally. It has been noted that when mixed with other minerals, quartz has a synergistic effect. This phenomenon is of practical importance because quartz in the workplace is rarely pure. Thus, miners may have more quartz in their lungs than some quartz-exposed workers and yet have relatively mild disease, which provides a protective effect.

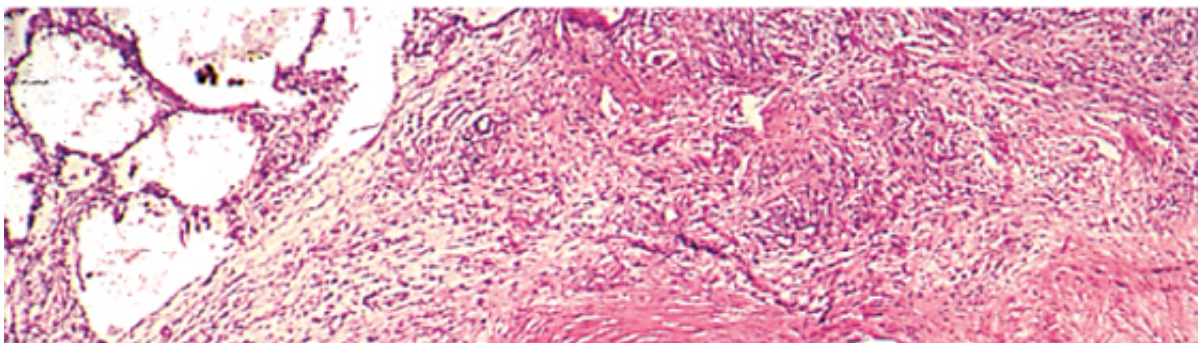
### Morphology

**Silicotic nodules** are characterized grossly in their early stages by tiny, barely palpable, blackened (if coal dust is also present) nodules in the upper zones of the lungs (Figure 20). The silicotic nodule demonstrates concentrically arranged hyalinized collagen fibers around an amorphous center. The "whorled" appearance of the collagen fibers is quite distinctive (Figure 20). Examination of the nodules by polarized microscopy reveals weakly birefringent collagen primarily in the center of the nodules. As the disease progresses, the individual nodules coalesce into large, hard, collagenous scars, with eventual progression to PMF. The intervening lung parenchyma is compressed or overexpanded, and a honeycomb pattern may develop. Fibrotic lesions involve the hilar lymph nodes and pleura. Sometimes, thin sheets of calcification occur in the lung parenchyma, appreciated radiographically as "eggshell" calcification (e.g., calcium surrounding a granuloma or calcification).

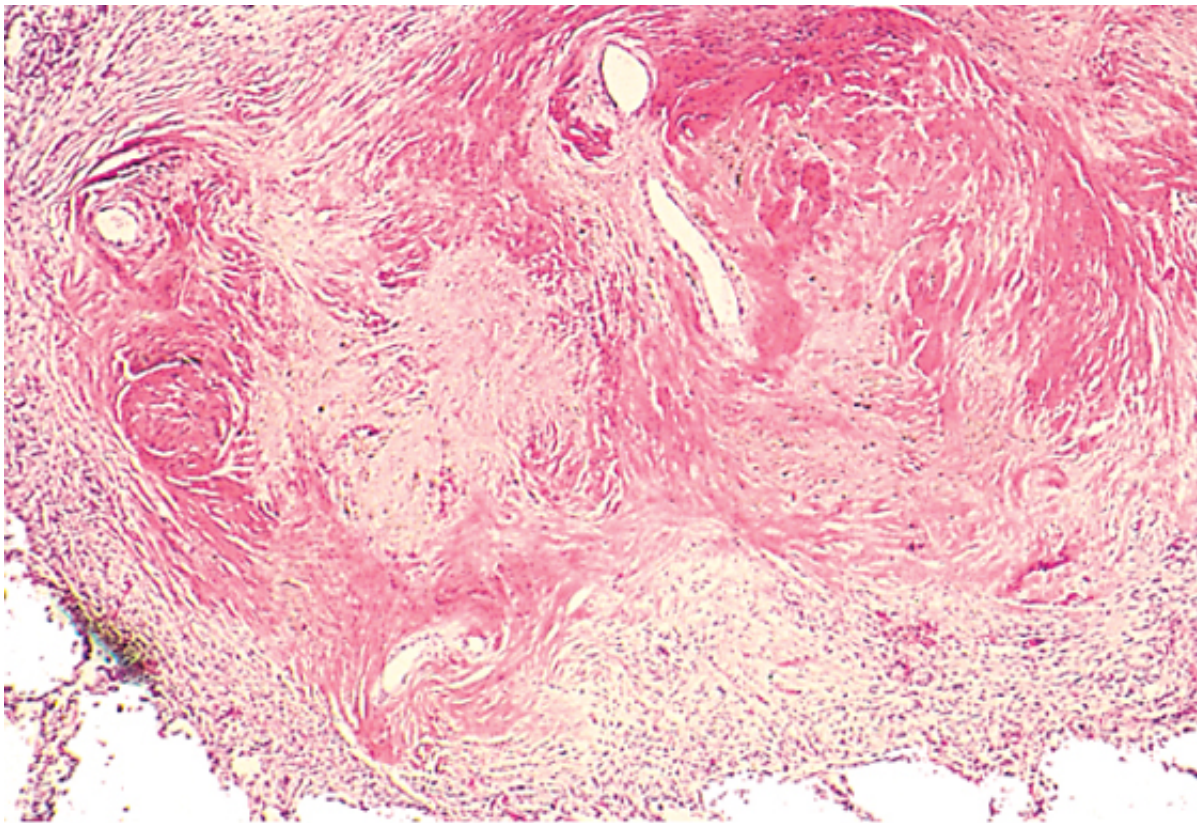




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Figure 13-19 Advanced silicosis seen on transection of lung. Scarring has contracted the upper lobe into a small, firm mass with extensive thickening. (Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston)







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Figure 13-20 Several coalescent collagenous silicotic nodules. (Courtesy of Dr. John Godleski, Brigham and V

### Clinical Course

Silicosis is usually detected in routine chest radiographs performed on asymptomatic workers. The nodularity in the upper zones of the lung, but pulmonary function is either normal or only moderately develop shortness of breath until late in the course, after PMF is present. At this time, the disease is no longer exposed. Many individuals with PMF develop pulmonary hypertension and cor pulmonale induced vasoconstriction and parenchymal destruction. The disease is slow to kill, but impaired physical activity. *Silicosis is associated with an increased susceptibility to tuberculosis.* It is postulated that mediated immunity, and crystalline silica may inhibit the ability of pulmonary macrophages to kill *P. tuberculosis*. silicotuberculosis often display a central zone of caseation. The relationship between silica and lung cancer, but in 1997, based on evidence from several epidemiologic studies, the International Agency for Research on Cancer (IARC) declared *crystalline silica* from occupational sources is carcinogenic in humans. However, this subject continues to be controversial.

### Asbestosis and Asbestos-Related Diseases

Asbestos is a family of crystalline hydrated silicates with a fibrous geometry. On the basis of epidemiologic data, exposure to asbestos is linked to (1) parenchymal interstitial fibrosis (*asbestosis*); (2) localized fibrous plaque; (3) pleural effusions; (4) bronchogenic carcinoma; (5) malignant pleural and peritoneal mesothelioma. The increased incidence of asbestos-related cancers in family members of asbestos workers has alerted the public to the hazards of asbestos in the environment.

### Pathogenesis

Concentration, size, shape, and solubility of the different forms of asbestos dictate whether disease develops. The two main types of asbestos are *serpentine* (in which the fiber is curly and flexible) and *amphibole* (in which the fiber is straight and stiff). The serpentine *chrysotile* accounts for most of the asbestos found in the environment. Amphiboles, even though less prevalent, are more pathogenic than the serpentine *chrysotile*, but *crocidolite* and *amosite* are associated with cancer, and mesothelioma. The greater pathogenicity of straight and stiff amphiboles is apparently due to their greater resistance to degradation. *Chrysotiles*, with their more flexible, curled structure, are likely to become impacted in the upper respiratory tract.

mucociliary elevator. Those that are trapped in the lungs are gradually leached from the tissues, but amphiboles. The straight, stiff amphiboles, in contrast, align themselves in the airstream and are trapped where they may penetrate epithelial cells and reach the interstitium. Despite these differences, both increasing exposure to either is associated with a higher incidence of all asbestos-related disease. Pneumoconioses, causes fibrosis by interacting with lung macrophages.

In addition to cellular and fibrotic lung reactions, asbestos probably also functions as both a tumor promoter and initiator. The oncogenic effects of asbestos on the mesothelium are mediated by reactive free radicals generated by the fibers. These fibers localize in the distal lung close to the mesothelial layer. However, potentially toxic chemicals also undoubtedly contribute to the pathogenicity of the fibers. For example, *the adsorption of carcinogenic fibers may well be important to the remarkable synergy between tobacco smoking and the development of lung cancer in asbestos workers.*

### Morphology

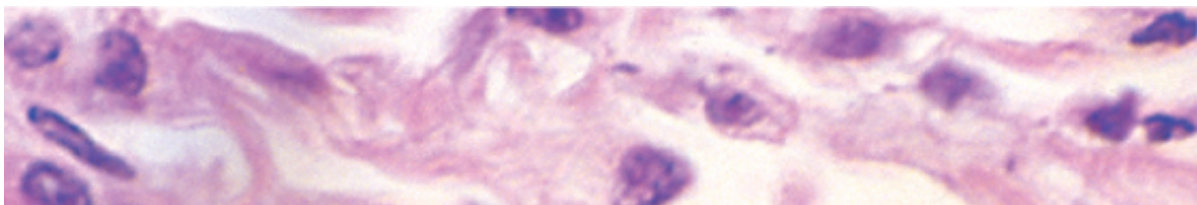
**Asbestosis** is marked by diffuse pulmonary interstitial fibrosis. These changes are those resulting from other causes of diffuse interstitial fibrosis, except for the presence of asbestos fibers which are seen as golden brown, fusiform or beaded rods with a translucent center. Asbestos fibers are often coated with an iron-containing proteinaceous material (Fig. 13-21). Asbestos fibers are phagocytosed by macrophages; the iron is derived from hemoglobin. Asbestos bodies can sometimes be found in the lungs of normal persons, but usually at low concentrations and without an accompanying interstitial fibrosis.

In contrast to CWP and silicosis, asbestosis begins in the lower lobes and subpleural regions. As the disease progresses, the upper lobes of the lungs become affected as fibrosis progresses. Contraction of the lung tissue distorts the native architecture, creating enlarged airspaces enclosed within thick fibrous walls. The subpleural regions become honeycombed. Simultaneously, the visceral pleura undergoes fibrosis and sometimes binds the lungs to the chest wall. The scarring may trap and narrow pulmonary arterioles, causing pulmonary hypertension and cor pulmonale.

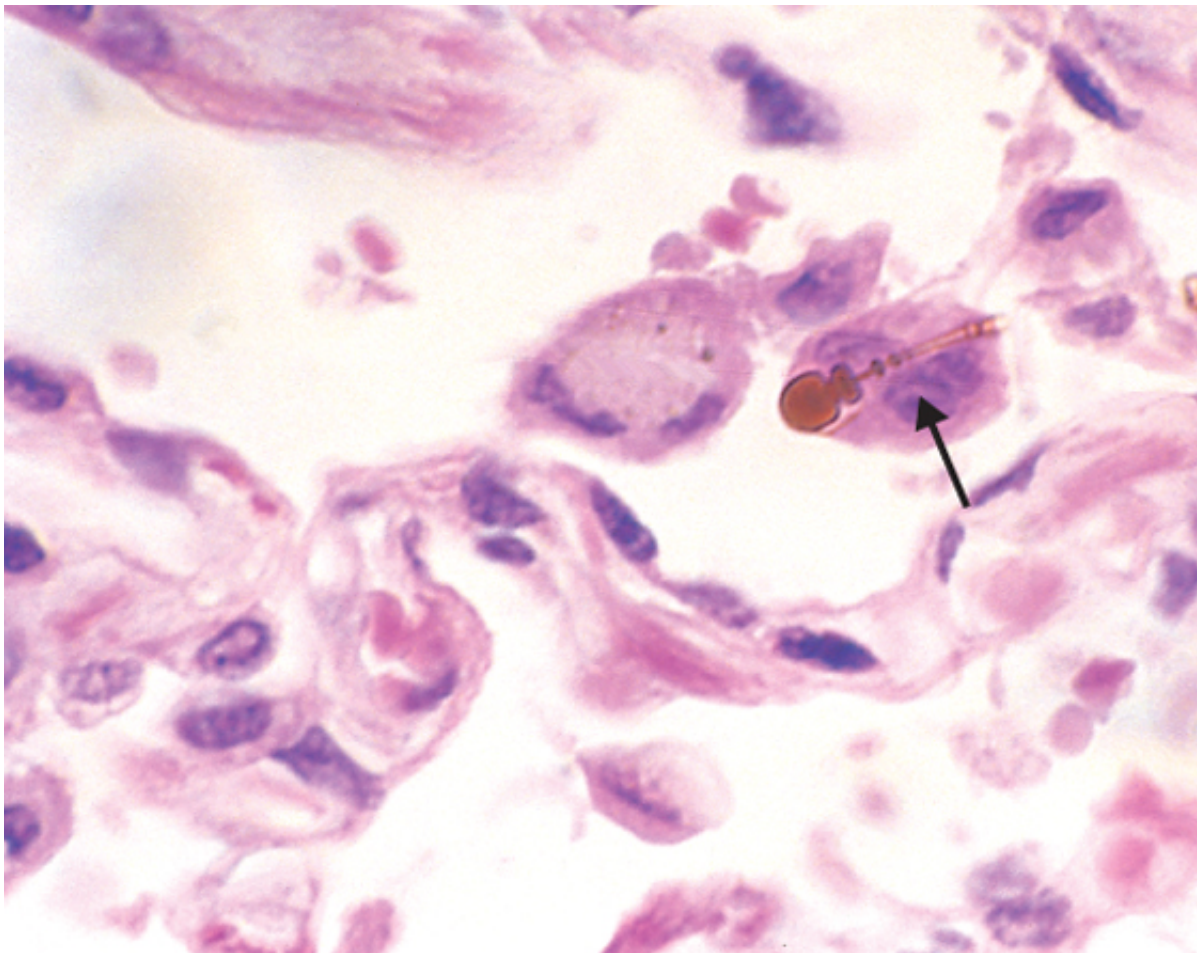
**Pleural plaques** are the most common manifestation of asbestos exposure and are composed of dense collagen (Fig. 13-22), often containing calcium. They develop on the anterior and posterolateral aspects of the **parietal pleura** and over the domes of the lungs. They contain asbestos bodies, and only rarely do they occur in persons who have no history of asbestos exposure. Uncommonly, asbestos exposure induces pleural effusions, which may be bloody. Rarely, diffuse visceral pleural fibrosis may occur and, in advanced cases, it may involve the thoracic cavity wall.

### Clinical Course

The clinical findings in asbestosis are indistinguishable from those of any other diffuse interstitial lung disease. Worsening dyspnea appears 10 to 20 years after exposure. The dyspnea is usually accompanied by a nonproductive cough and sputum. The disease may remain static or progress to CHF, cor pulmonale, and death. Pleural plaques are detected on radiographs as circumscribed densities. *Both bronchogenic carcinomas and malignant mesotheliomas are exposed to asbestos.* The risk of bronchogenic carcinoma is increased about fivefold for asbestos exposure. Mesotheliomas, normally a very rare tumor (2-17 cases per 1 million persons), is more than 1000-fold increased in persons with asbestos exposure. Concomitant cigarette smoking greatly increases the risk of bronchogenic carcinoma but not that of mesothelioma. Lung or pleural cancer associated with asbestos exposure is usually diagnosed in the advanced stages.







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Figure 13-21 High-power detail of an asbestos body, revealing the typical beading and l

## SUMMARY

**Pneumoconioses** Pneumoconioses encompass a group of chronic fibrosing resulting from exposure to organic and inorganic particulates, most common alveolar macrophages play a central role in the pathogenesis of lung injury and producing reactive oxygen species and fibrogenic cytokines. Coal dust-induced from *asymptomatic anthracosis*, to *simple coal workers pneumoconiosis* (COPD and centrilobular emphysema), to progressive massive fibrosis (PMF), manifesting pulmonary dysfunction, pulmonary hypertension, and cor pulmonale. Silicosis is the most common pneumoconiosis in the world, and crystalline silica (e.g., quartz) is the usual cause. Manifestations of silicosis can range from asymptomatic silicotic nodules to severe fibrosis. Silicosis also has an increased susceptibility to tuberculosis. The relationship between exposure and subsequent lung cancer is controversial. Asbestos fibers, commonly *amphiboles*, have a greater fibrogenic and carcinogenic potential than the *chrysotiles*. Asbestos exposure is linked with six disease processes: (1) parenchymal fibrosis (*asbestosis*); (2) localized fibrous plaques or, rarely, diffuse pleural thickening; (3) pleural effusions; (4) lung cancer; (5) malignant pleural and peritoneal mesothelioma; and (6) cancer. Cigarette smoking increases the risk of lung cancer in the setting of asbestos exposure. Moreover, even family members of workers exposed to asbestos are at increased risk.

## Drug- and Radiation-Induced Pulmonary Diseases

Drugs and radiation can induce pulmonary diseases. The most common drug-induced pulmonary diseases are hypersensitivity pneumonitis and drug-induced lung injury. Radiation-induced pulmonary diseases include radiation pneumonitis and radiation-induced lung cancer.

Drugs can cause a variety of both acute and chronic alterations in respiratory structure and function. For example, the anticancer agent, *bleomycin*, causes pneumonitis and interstitial fibrosis, as a result of direct toxicity of the drug and recruitment of inflammatory cells into the alveoli. Similarly, *amiodarone*, an anti-arrhythmic agent, is also associated with lung toxicity. *Radiation pneumonitis* is a well-known complication of therapeutic radiation of pulmonary and other organs. *Radiation pneumonitis*, which typically occurs 1 to 6 months after therapy in as many as 20% of individuals, is characterized by inflammation, proportion to the volume of irradiated lung, pleural effusion, and pulmonary infiltrates corresponding to the volume of irradiated lung. Symptoms may resolve with corticosteroid therapy or progress to *chronic radiation pneumonitis*, a

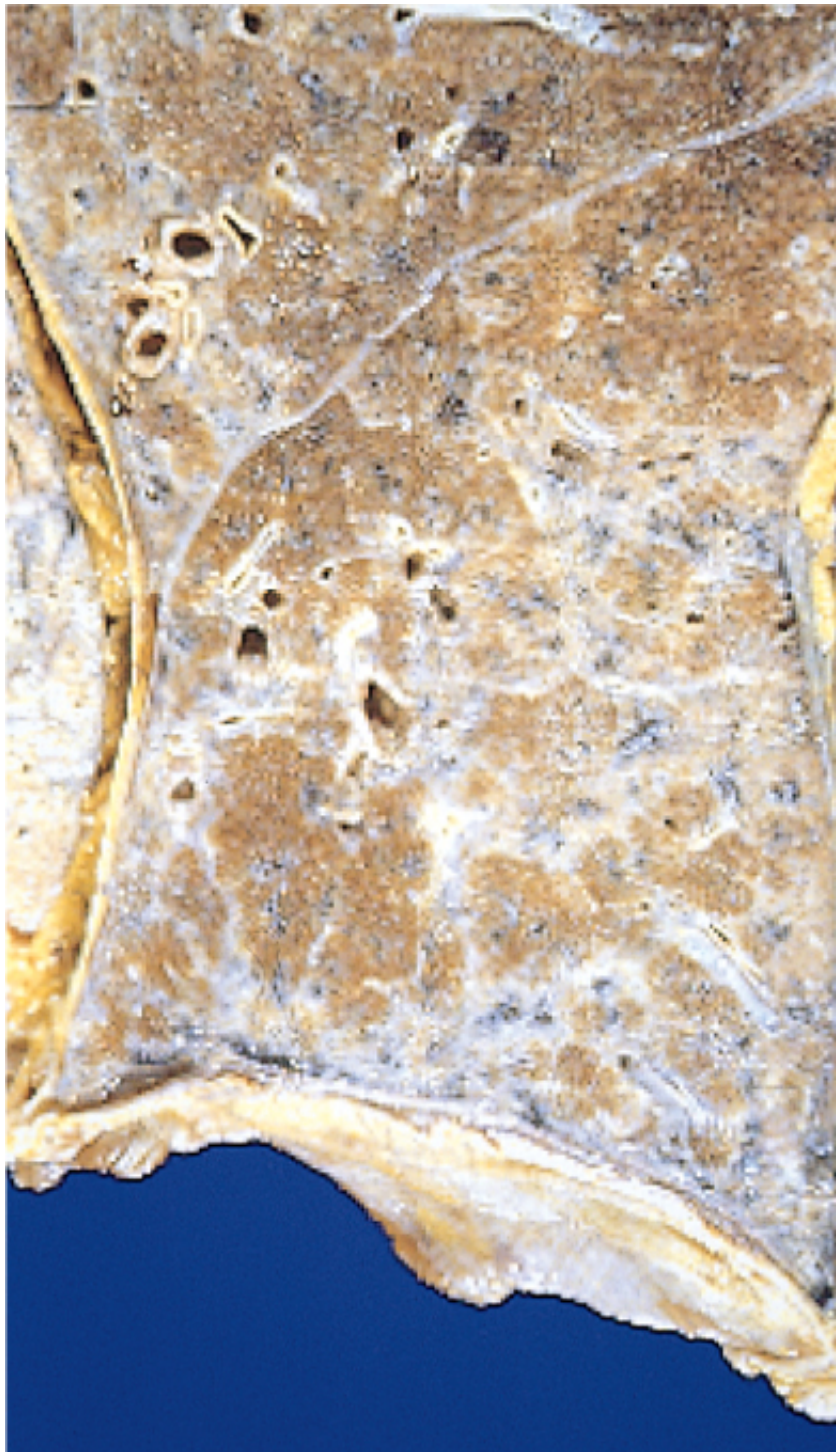


Figure 13-22 Asbestosis. Markedly thickened visceral pleura covers the lateral and diaphragmatic surface of lung, affecting the lower lobe of the lung.

## Granulomatous Diseases

### Sarcoidosis

Although sarcoidosis is considered here as an example of a restrictive lung disease, it is important to recognize that it is a *multisystem disease of unknown etiology characterized by noncaseating granulomas in many tissues*. Including mycobacterial or fungal infections and berylliosis, sometimes also produce noncaseating granulomas. The *diagnosis of sarcoidosis is one of exclusion*. Although the multisystemic involvement of sarcoidosis is common, bilateral hilar lymphadenopathy or lung involvement (or both), visible on chest radiographs, is the most common. Eye and skin involvement each occurs in about 25% of cases and may occasionally be the presenting feature.

#### Epidemiology

Sarcoidosis occurs throughout the world, affecting both sexes and all races and ages. There are, however, epidemiologic trends, including the following:

There is a consistent predilection for adults younger than 40 years of age. A high incidence is seen in Swedish populations and among US African Americans (in whom the frequency of involvement is higher than in Caucasians). Sarcoidosis is one of the few pulmonary diseases with a higher prevalence in African Americans.

#### Etiology and Pathogenesis

Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a dysregulation in genetically predisposed individuals exposed to certain environmental agents. The role of these influences is summarized below.

There are several *immunologic abnormalities* in sarcoidosis that suggest the development of a cell-mediated immune response. The process is driven by CD4<sup>+</sup> helper T cells. These include:

Intra-alveolar and interstitial accumulation of CD4<sup>+</sup> T<sub>H</sub>1 cells. Oligoclonal expansion of T-cell receptor rearrangement. Increases in T cell-derived T<sub>H</sub>1 cytokines such as IL-2 and interferon-γ, which promote macrophage activation, respectively. Increases in several cytokines in the local environment (e.g., tumor necrosis factor-α) that favor recruitment of additional T cells and monocytes and contribute to the common skin test antigens such as *Candida* or purified protein derivative (PPD), that may lead to CD4<sup>+</sup> T cells and consequent peripheral depletion. Polyclonal hypergammaglobulinemia, a dysregulation. Genetic influences in individuals with sarcoidosis are suggested by familial association with certain human leukocyte antigen (HLA) genotypes (e.g., class II HLA-A1 and HLA-B8).

Finally, several putative "antigens" have been proposed as the inciting agent for sarcoidosis (e.g., silica, aluminum, and organic dusts), but thus far *there is no unequivocal evidence to suggest that sarcoidosis is caused by an infectious agent*.

#### Morphology

The histopathologic sine qua non of sarcoidosis is the **noncaseating epithelioid granuloma** in the organ involved (Fig. 13-23). This is a discrete, compact collection of epithelioid cells, a zone of largely CD4<sup>+</sup> T cells. The epithelioid cells are derived from macrophages and have an abundant eosinophilic cytoplasm and vesicular nuclei. It is not uncommon to see multinucleated giant cells formed by fusion of macrophages. A thin layer of laminated fibroblasts is also present in the granuloma; over time, these proliferate and lay down collagen that replaces the epithelioid cells with a hyalinized scar. Two other microscopic features are sometimes seen in the granuloma: (1) **asteroid bodies**, laminated concretions composed of calcium and proteins; and (2) **asteroid inclusions** enclosed within giant cells. Their presence is not required for diagnosis, as they also occur in granulomas of other origins. Rarely, foci of central necrosis may be present in the granulomas, suggesting an infectious process. Caseation necrosis is typical of tuberculosis.



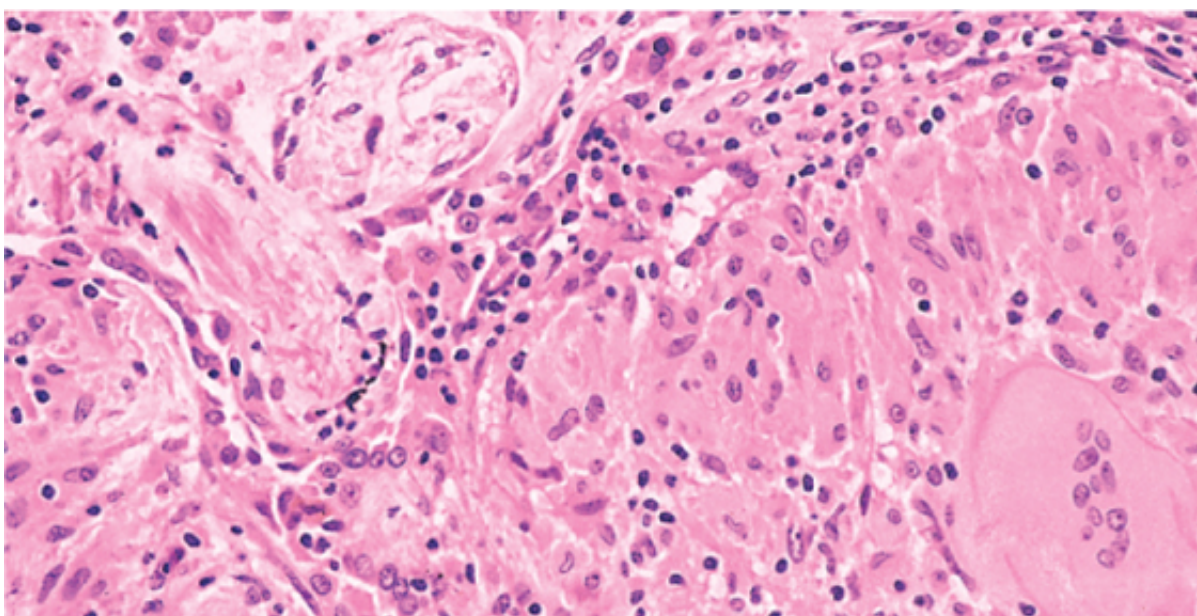
The **lungs** are involved at some stage of the disease in 90% of patients. The granulomas involve the interstitium rather than airspaces, with some tendency to localize in the bronchioles and pulmonary venules and in the pleura ("lymphangitic" distribution). Bronchoalveolar lavage (BAL) contains abundant CD4+T cells. In 5% to 15% of patients, the granuloma is replaced by **diffuse interstitial fibrosis** resulting in a honeycomb lung.

Intrathoracic **hilar and paratracheal lymph nodes** are enlarged in 75% to 90% of patients, often present with peripheral lymphadenopathy. The nodes are characteristically painless and have a rubbery texture. Unlike in tuberculosis, lymph nodes in sarcoidosis are "nonmatted" (nonadherent and do not ulcerate).

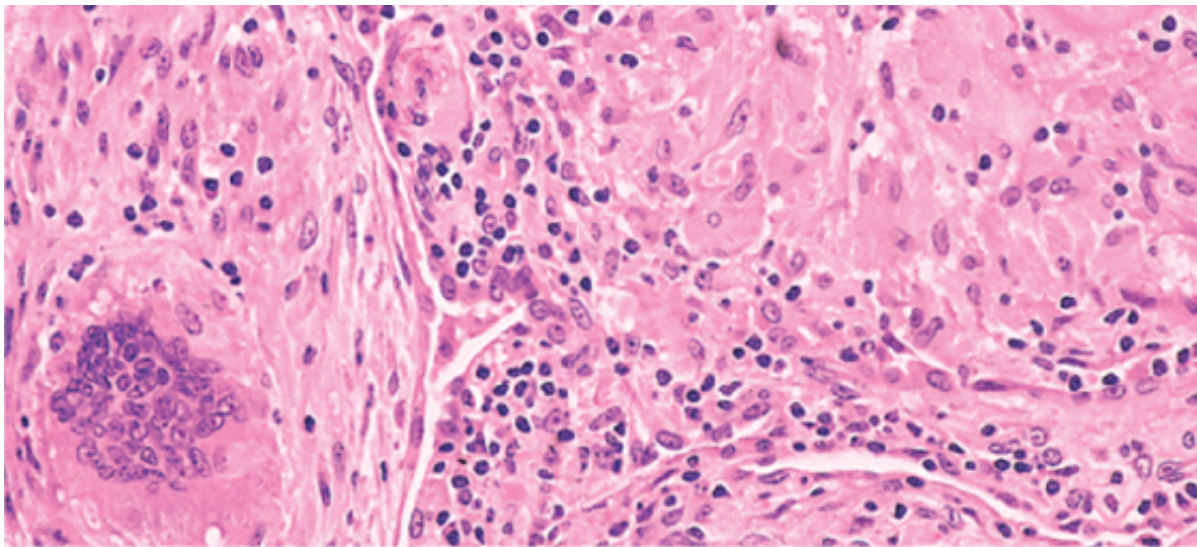
**Skin lesions** are encountered in approximately 25% of patients. **Erythema nodosum**, a form of sarcoidosis, consists of raised, red, tender nodules on the anterior aspects of the lower extremities. Calcifications are uncommon in these lesions. In contrast, discrete painless subcutaneous nodules are characteristic of sarcoidosis, and these usually reveal abundant noncaseating granulomas. Another form of sarcoidosis consists of indurated plaques associated with a violaceous discoloration of the nose, cheeks, and lips (**lupus pernio**).

**Involvement of the eye and lacrimal glands occurs in about one-fifth to one-third of patients.** Ocular involvement takes the form of iritis or iridocyclitis and may be unilateral or bilateral. Corneal opacities, glaucoma, and (less commonly) total loss of vision may develop. The optic nerve is also affected, with resultant **choroiditis, retinitis, and optic nerve involvement**, frequently accompanied by inflammation in the lacrimal glands, with suppression of lacrimation (**Sjögren's syndrome**). **Unilateral or bilateral parotitis with painful enlargement of the parotid glands** occurs in less than 10% of the individuals with sarcoidosis; some go on to develop xerostomia. **Unilateral or bilateral submandibular gland involvement** is designated **Mikulicz syndrome**.

**The spleen** may appear unaffected grossly, but in about three-fourths of cases it becomes clinically enlarged. **The liver** demonstrates microscopic lesions, usually in the portal triads, about as often as the spleen, but only about 10% of patients demonstrate hepatomegaly or abnormal liver function. Sarcoid involvement of **bone** occurs in as many as 40% of patients, although it rarely causes severe manifestations. Sometimes it causes hypercalciuria. This is not related to bone destruction but rather is caused by increased calcium absorption secondary to production of active vitamin D by the mononuclear phagocyte system.







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Figure 13-23 Characteristic sarcoid noncaseating granulomas in lung with many giant cells. (Courtesy of Dr. Ramo Women's Hospital, Boston, Massachusetts.)

### *Clinical Course*

In many individuals the disease is entirely asymptomatic, discovered on routine chest films as bilateral hilar lymphadenopathy. In others, peripheral lymphadenopathy, cutaneous lesions, eye involvement, and other systemic manifestations. In about two-thirds of symptomatic cases there is a gradual appearance of symptoms (cough, breath, dry cough, or vague substernal discomfort) or constitutional signs and symptoms (fever, fatigue, weight loss, and night sweats). Because of the variable and nondiagnostic clinical features, resort is frequently made to histopathologic examination. *of noncaseating granulomas is suggestive of sarcoidosis, but other identifiable causes of granulomatous disease must be excluded.*

Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periodic remissions. The remissions may be spontaneous or initiated by steroid therapy and are often permanent. In many individuals recover with minimal or no residual manifestations. Twenty percent develop permanent disability. Of the remaining 10% to 15%, most succumb to progressive pulmonary fibrosis and cor pulmonale.

### **SUMMARY**

**Sarcoidosis** Multisystemic disease of unknown etiology; histopathologic significance is the presence of noncaseating granulomas in various tissues. Immunologic abnormalities include high levels of serum angiotensin-converting enzyme (ACE) and locally produced cytokines such as IFN- $\gamma$  and IL-2. Clinical manifestations include lymph node enlargement, eye involvement (sicca syndrome [dry eye], uveitis), skin lesions (erythema nodosum, lupus pernio), and visceral (liver, skin, heart, and nervous system) involvement occurs in 90% of cases with formation of granulomas and interstitial fibrosis.

### **Hypersensitivity Pneumonitis**

Hypersensitivity pneumonitis is an immunologically mediated inflammatory lung disease that primarily affects the alveoli, often called *allergic alveolitis*. Most often it is an occupational disease that results from heightened sensitivity to inhaled antigens such as moldy hay (Table 13-5). Unlike bronchial asthma, in which *bronchi are the focus of immunological hypersensitivity pneumonitis occurs at the level of alveoli*. Hence, it presents as a predominantly restrictive lung disease with decreased lung diffusion capacity, lung compliance, and total lung volume. The occupational exposures are diverse, and the clinical and pathologic findings and probably have very similar pathophysiology.

Several lines of evidence suggest that hypersensitivity pneumonitis is an immunologically mediated disease.

Bronchioalveolar lavage specimens consistently demonstrate increased numbers of T lymphocyte phenotype. Most individuals with hypersensitivity pneumonitis have specific precipitating antigens and immunoglobulins have been demonstrated within vessel walls by immunofluorescence. The presence of noncaseating granulomas in two-thirds of individuals with this disorder suggests hypersensitivity against the implicated antigen(s).

In summary, hypersensitivity pneumonitis is an immunologically mediated response to an extrinsic antigenic complex and delayed-type hypersensitivity reactions.

**Table 13-5. Selected Causes of Hypersensitivity Pneumonitis**

Syndrome	Exposure	Antigens
<b>Fungal and Bacterial Antigens</b>		
Farmer's lung	Moldy hay	<i>Micropolyspora faeni</i>
Bagassosis	Moldy pressed sugar cane (bagasse)	Thermophilic actinomycetes
Maple bark disease	Moldy maple bark	<i>Cryptostroma corticale</i>
Humidifier lung	Cool-mist humidifier	Thermophilic actinomycetes
Malt worker's lung	Moldy barley	<i>Aspergillus clavatus</i>
Cheese washer's lung	Moldy cheese	<i>Penicillium casei</i>
<b>Insect Products</b>		
Miller's lung	Dust-contaminated grain	<i>Sitophilus granarius</i> (wheat)
<b>Animal Products</b>		
Pigeon breeder's lung	Pigeons	Pigeon serum proteins in droppings
<b>Chemicals</b>		
Chemical worker's lung	Chemical industry	Trimellitic anhydride, isocyanates

### **Morphology**

The histopathology of both acute and chronic forms of hypersensitivity pneumonitis shows mononuclear cell infiltrates in the pulmonary interstitium, with a characteristic peribronchovascular pattern. Lymphocytes predominate, but plasma cells and epithelioid cells are also present. In the chronic disease, variable numbers of neutrophils also may be seen. **Interstitial noncaseating granulomas** are present in more than two-thirds of cases, usually in a peribronchiolar location. In the chronic form, diffuse interstitial fibrosis occurs.

### **Clinical Course**

Hypersensitivity pneumonitis may present either as an *acute reaction* with fever, cough, dyspnea, and malaise, hours after exposure or as a *chronic disease* with insidious onset of cough, dyspnea, malaise, and weight loss. In the acute form of this disease is usually obvious because of the temporal relationship of symptoms to exposure. If the antigenic exposure is terminated after acute attacks of the disease, there is complete resolution of symptoms. Failure to remove the inciting agent from the environment eventually results in a chronic interstitial pneumonia with exacerbations seen on antigen re-exposure.

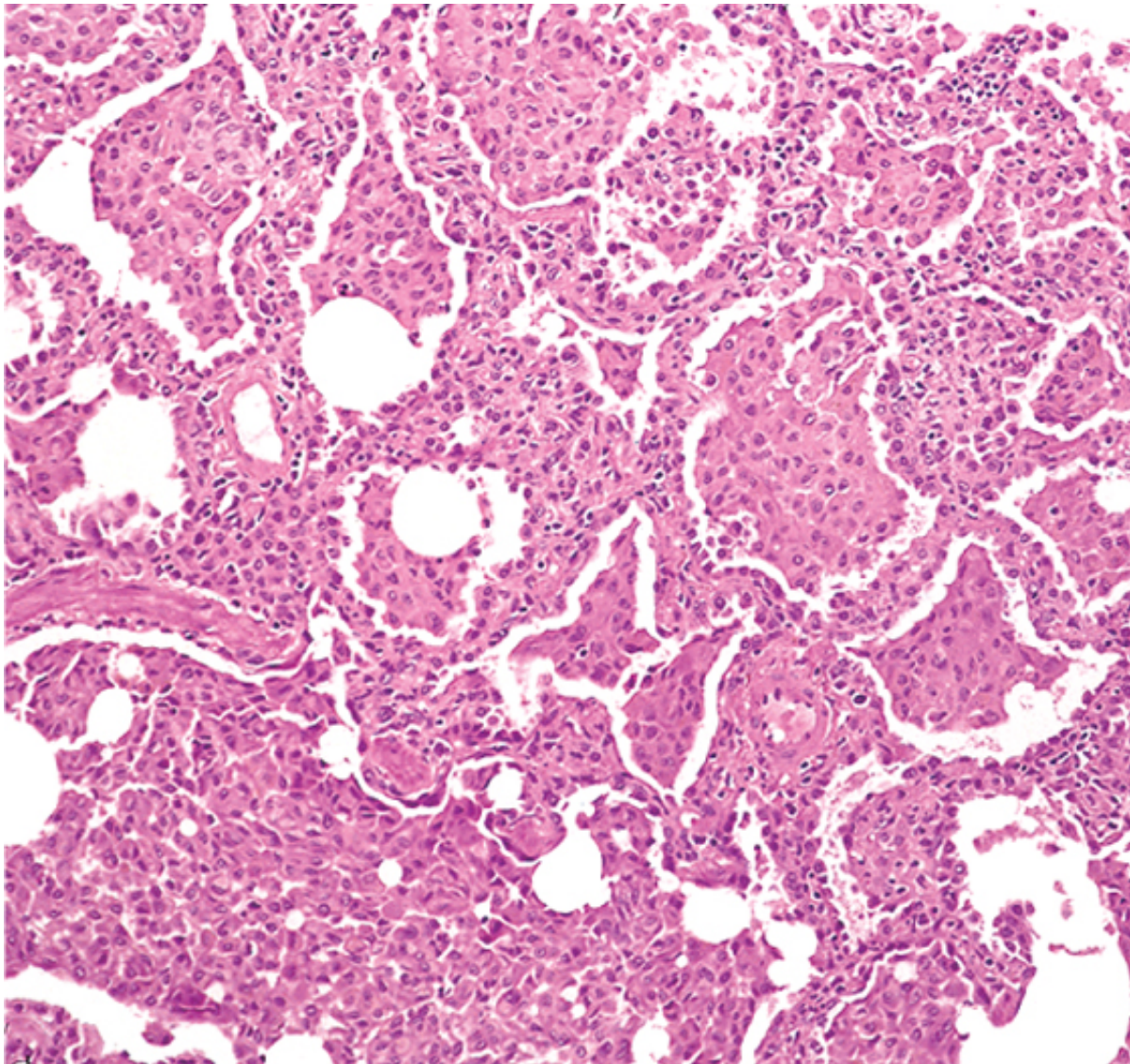
### **Pulmonary Eosinophilia**

A number of clinical and pathologic pulmonary entities are characterized by an infiltration and activation of eosinophils and elevated levels of alveolar IL-5. These diverse diseases are generally of immunologic origin, but acute eosinophilia is divided into the following categories:

*Acute eosinophilic pneumonia with respiratory failure*, characterized by rapid onset of fever, cough, dyspnea, and pulmonary infiltrates on chest radiographs. The bronchioalveolar lavage fluid typically contains many eosinophils and a prompt response to corticosteroids. *Simple pulmonary eosinophilia* (Löffler syndrome), characterized by transient eosinophilia in the blood, and a benign clinical course. The alveolar septa are thickened by

occasional giant cells. *Tropical eosinophilia*, caused by infection with microfilariae, a parasitic example, in association with asthma, drug allergies, and certain forms of vasculitis. *Idiopathic* characterized by aggregates of lymphocytes and eosinophils within the septal walls and the periphery of the lung fields, and accompanied by high fever, night sweats, and dyspnea. The causes of pulmonary eosinophilia have been ruled out.

### Smoking-Related Interstitial Diseases



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Figure 13-24 Desquamative interstitial pneumonia. Medium-power detail of lung to demonstrate the accumulation of macrophages in the alveolar spaces with only mild fibrous thickening of the alveolar wall

The role of cigarette smoking in causing obstructive pulmonary disease (emphysema and chronic bronchitis) is well established. Smoking is also associated with restrictive or interstitial lung diseases. *Desquamative interstitial pneumonia* and *chronic eosinophilic pneumonia* are the two related examples of smoking-associated interstitial lung disease. The most striking histologic feature is the presence of large numbers of macrophages with abundant cytoplasm containing dusty brown pigment (*smoke macrophages*). The alveolar septa are thickened by a sparse inflammatory infiltrate (usually lymphocytes) and occasional plasma cells. Pulmonary functions usually show a mild restrictive abnormality, and patients with DIP typically respond to steroid therapy and smoking cessation. Respiratory bronchiolitis is a common histologic



by the presence of pigmented intraluminal macrophages akin to DIP, but in a "bronchiolocentric" (respiratory bronchioles). Mild peribronchiolar fibrosis is also seen. As with DIP, individuals present with cough, and the symptoms recede with cessation of smoking.



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## DISEASES OF VASCULAR ORIGIN

### Pulmonary Embolism, Hemorrhage, and Infarction

Blood clots that occlude the large pulmonary arteries are almost always embolic in origin. More than half of these clots originate from thrombi within the large deep veins of the lower legs, typically originating in the popliteal vein. Thromboembolism causes approximately 50,000 deaths per year in the United States. Even when the course of other diseases. The true incidence of nonfatal pulmonary embolism is not known. Some emboli are small and clinically silent. Even among hospitalized individuals, many are small and clinically silent. Autopsy data on the incidence of pulmonary emboli vary widely, ranging from 10% in the general population, to 30% in individuals dying after severe burns, trauma, or fractures. The influences that affect the legs were discussed in [Chapter 4](#), but the following risk factors should be emphasized: (1) prolonged immobilization of the legs, (2) surgery, especially orthopedic surgery, of knee and hip, (3) severe trauma, (4) congestive heart failure, (5) women in the period around parturition or who take birth control pills, (6) disseminated cancer, and (7) primary disorders of hypercoagulability (e.g., factor V Leiden; see [Chapter 10](#)).

The pathophysiologic consequences of thromboembolism in the lung depend largely on the size and location of the occluded pulmonary artery, and on the cardiopulmonary status of the patient. There are three major consequences of pulmonary arterial occlusion: (1) an increase in pulmonary artery pressure from blockage of flow and the release of mediators (e.g., thromboxane  $A_2$  and serotonin); and (2) a decrease in pulmonary perfusion of the lung parenchyma. Thus, occlusion of a *major vessel* results in a sudden increase in pulmonary artery pressure, right-sided heart failure (*acute cor pulmonale*), or even death. Usually hypoxemia develops.

*Perfusion of lung zones that have become atelectatic.* The alveolar collapse occurs in the dependent zones of the lung because of poor surfactant production and because pain associated with embolism leads to reduced movement of the chest wall. If the pulmonary blood flow is redirected through areas of the lung that are normally hypoxic, it causes a *widening of the difference in arterial-venous oxygen saturation*. *Right-to-left shunt* occurs through a patent foramen ovale, present in 30% of normal individuals. If *smaller vessels* are occluded, the event may even be clinically silent.

Recall that lung is oxygenated not only by the pulmonary arteries but also by bronchial arteries. If the bronchial circulation is normal and adequate ventilation is maintained, the resultant decrease in blood flow is not significant. Indeed, ischemic necrosis (infarction) resulting from pulmonary thromboembolism is the exception as 10% of cases. It occurs only if there is compromise in cardiac function or bronchial circulation, or if the lung is underventilated as a result of underlying pulmonary disease.

### Morphology

The morphologic consequences of pulmonary embolism, as noted, depend on the size and location of the embolus and the general state of the circulation. Large emboli impact in the main pulmonary branches or lodge astride the bifurcation as a **saddle embolus** ([Fig. 13-25](#)). Death results suddenly from hypoxia or acute failure of the right side of the heart (acute cor pulmonale). Time for morphologic alterations in the lung. Smaller emboli become impacted in medium-sized pulmonary arteries. With adequate circulation and bronchial arterial flow, the vitality of the lung is maintained, but the alveolar spaces may fill with blood to produce pulmonary hemorrhage and ischemic damage to the endothelial cells.

With compromised cardiovascular status, as may occur with congestive heart failure, the more peripheral the embolic occlusion, the more likely is infarction. About three-fourths of the infarcts involve the lower lobes, and more than half are multiple. Characteristically, they are wedge-shaped, with the apex pointing toward the hilus of the lung. Pulmonary infarction is hemorrhagic and appears as raised, red-blue areas in the early stages ([Fig. 13-26](#)).

surface is often covered by a fibrinous exudate. If the occluded vessel can be identified near the apex of the infarcted area. The red cells begin to lyse within 48 hours, and eventually becoming red-brown as hemosiderin is produced. In time, fibrous replacement margins as a gray-white peripheral zone and eventually converts the infarct into a scar below the level of the lung substance. Histologically, the hallmark of fresh infarcts is the lung parenchyma in the area of hemorrhage.

#### *Clinical Course*

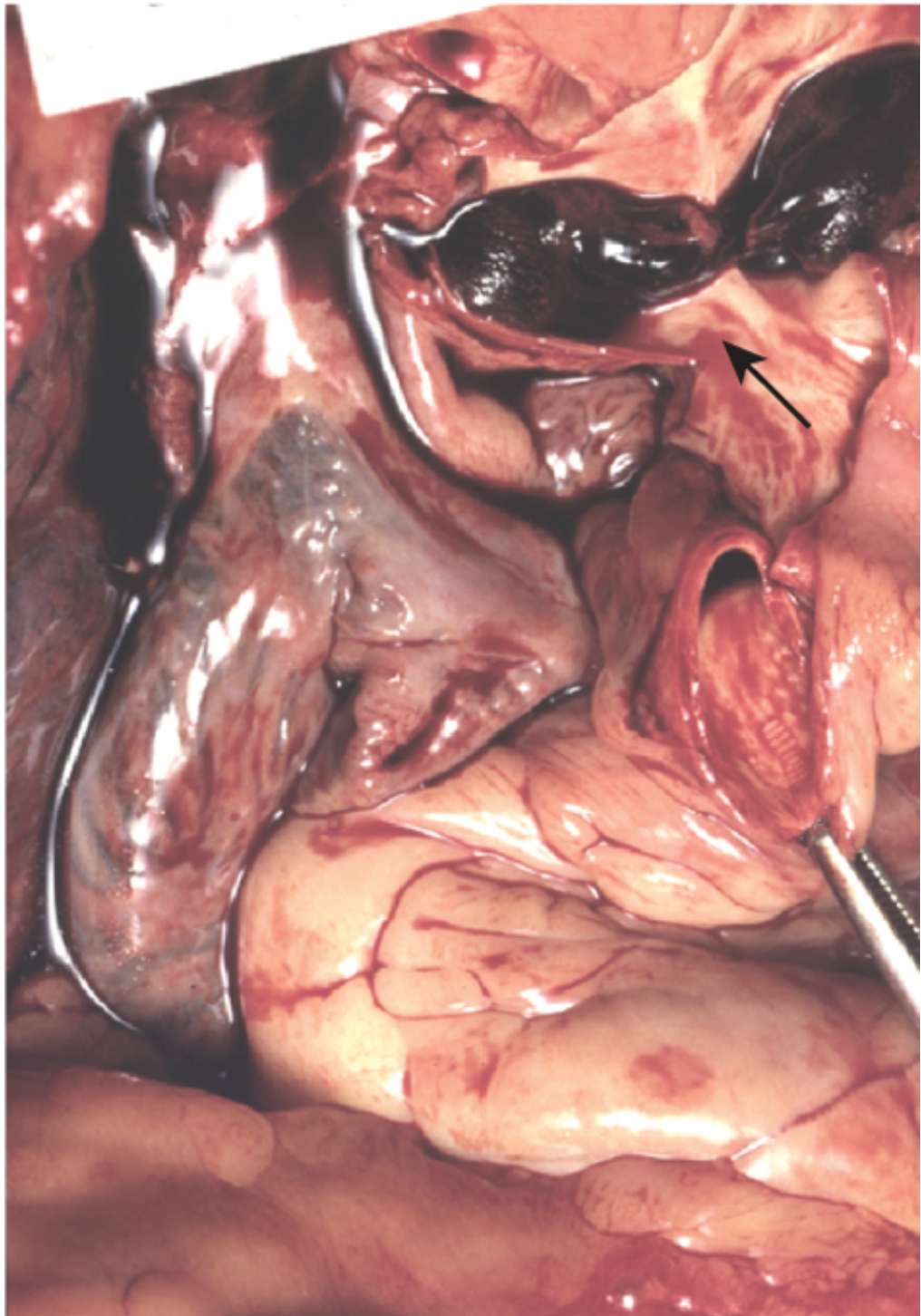




Figure 13-25 Large saddle embolus from the femoral vein lying astride the main left and right pulmonary arteries.  
Pathology, University of Texas Southwestern Medical School, Dallas, T

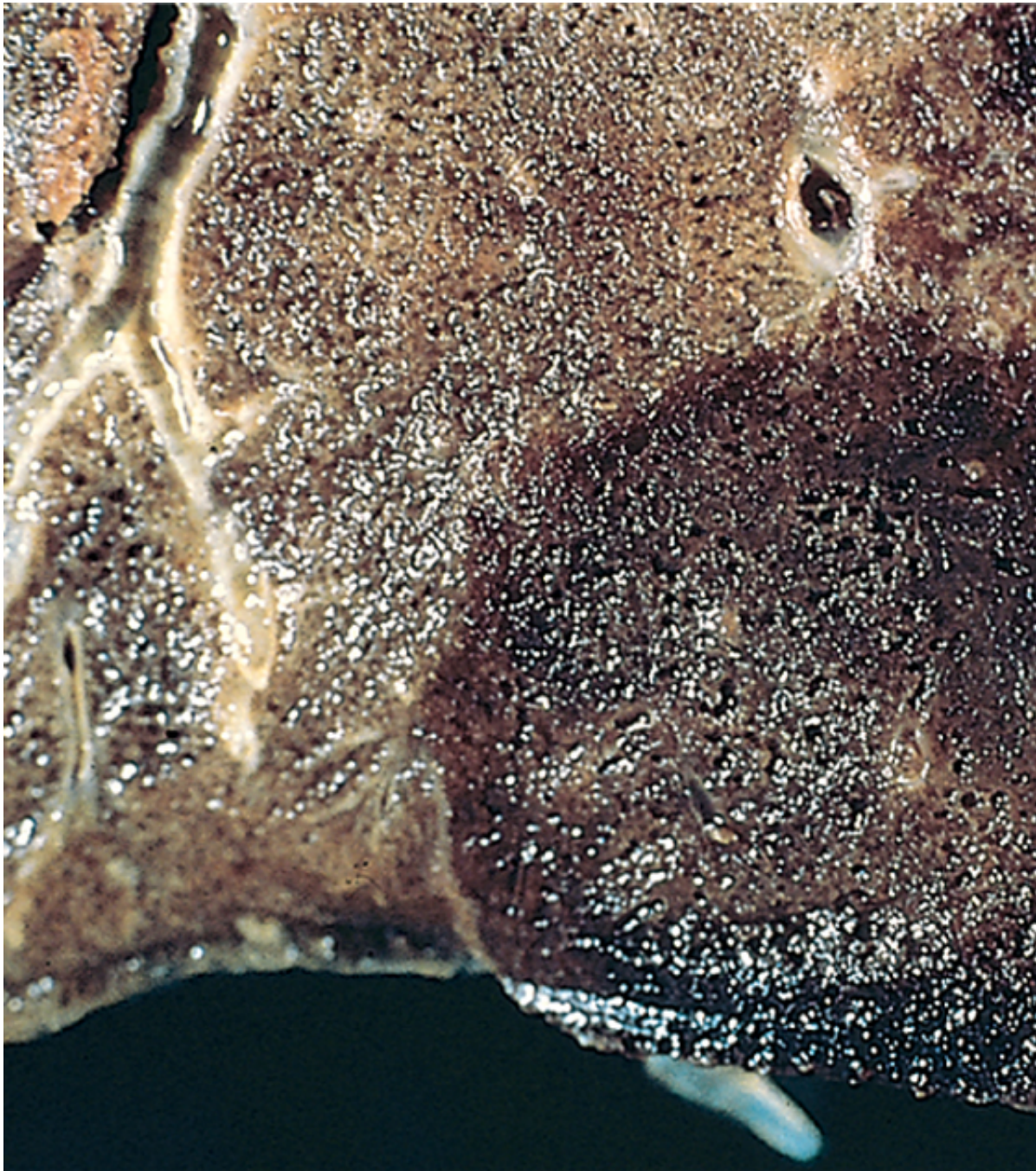


Figure 13-26 A recent small, roughly wedge-shaped hemorrhagic pulmona

The clinical consequences of pulmonary thromboembolism are summarized here:

Most pulmonary emboli (60% to 80%) are clinically silent because they are small; the embolus is absorbed, and the bronchial circulation sustains the viability of the affected lung parenchyma

sudden death, acute right-sided heart failure (acute cor pulmonale), or cardiovascular collapse. 60% of the total pulmonary vasculature is obstructed by a large embolus or multiple simultaneous emboli. Massive pulmonary embolism is one of the few causes of literally instantaneous death, even before the person experiences dyspnea. Obstruction of relatively small to medium pulmonary branches (10% to 15% of cardiac output) causes pulmonary infarction when some element of circulatory insufficiency is present. Typically, dyspnea, the basis of which is not fully understood. In a small but significant subset of persons, pulmonary embolism leads to pulmonary hypertension, chronic right-sided heart strain (chronic cor pulmonale), and, in some cases, progressively worsening dyspnea.

Emboli usually resolve after the initial acute insult. They contract, and endogenous fibrinolytic activity eventually dissolves them. However, in the presence of an underlying predisposing factor, a small innocuous embolus may persist. *Patients who have experienced one pulmonary embolism have a 30% chance of developing a second.* Thus, repeat treatment are essential. Prophylactic therapy includes early ambulation for postoperative and post-traumatic patients, intermittent pneumatic compression and isometric leg exercises for bedridden patients. Anticoagulation therapy is essential. Patients with pulmonary embolism are given anticoagulation therapy. Patients with massive pulmonary embolism may require thrombolytic therapy.

In passing, mention should be made of nonthrombotic forms of pulmonary embolism, which include air embolism, fat embolism, and amniotic fluid embolism, which were discussed previously. Air embolism is often associated with foreign body embolism in the pulmonary microvasculature; the presence of air in the intravenous mixture elicits a granulomatous response within the interstitium or pulmonary arteries, leading to fibrosis, while the latter leads to pulmonary hypertension. Residual talc crystals can be demonstrated with polarized light. Bone marrow embolism (presence of hematopoietic and fat elements within pulmonary vasculature) occurs after trauma and in patients with bone infarction secondary to sickle cell anemia.

## SUMMARY

**Pulmonary Embolism** Almost all large pulmonary artery thrombi are emboli that originate from the deep veins of the lower leg. Risk factors include prolonged bedrest, surgery, trauma, CHF, oral contraceptives (especially those containing high estrogen), and genetic diseases of hypercoagulability. The vast majority (60% to 80%) of pulmonary emboli are asymptomatic (silent), a minority (5%) cause acute cor pulmonale, shock, or death (typically massive pulmonary embolism), and the remaining cause pulmonary infarction. Individuals who have experienced a pulmonary embolism are at high risk for recurrences.

## Pulmonary Hypertension

The pulmonary circulation is normally one of low resistance, with pulmonary blood pressures being lower than systemic blood pressure. Pulmonary hypertension (when mean pulmonary pressures reach one-fourth or more of systemic blood pressure) can be primary or secondary. Causes of secondary pulmonary hypertension include:

*Chronic obstructive or interstitial lung disease*, which is accompanied by destruction of lung parenchyma and alveolar capillaries. This causes increased pulmonary arterial resistance and secondarily pulmonary hypertension. *Pulmonary emboli*, which lead to a reduction in the functional cross-sectional area of the pulmonary vasculature, causing increased vascular resistance. *Antecedent heart disease*, for example, *mitral stenosis*, which causes increased pulmonary venous pressures, and ultimately pulmonary arterial hypertension. *Congenital heart disease* is another cause of secondary pulmonary hypertension.

Uncommonly, pulmonary hypertension exists even though all known causes of increased pulmonary vascular resistance have been excluded. This is referred to as *primary, or idiopathic, pulmonary hypertension*. Of these, the vast majority of cases are familial form with an autosomal dominant mode of inheritance.

## Pathogenesis



According to current thinking, *pulmonary endothelial cell and/or vascular smooth muscle dysfunction* is the basis for most forms of pulmonary hypertension.

In states of *secondary pulmonary hypertension*, endothelial cell dysfunction arises as a consequence (e.g., shear and mechanical injury due to increased blood flow in left-to-right shunts, or bioactive substances from recurrent thromboembolism). Endothelial cell dysfunction reduces production of vasodilators while increasing synthesis of vasoconstrictive mediators like endothelin. In addition, there are cytokines that induce the migration and replication of vascular smooth muscle and elaborate *pulmonary hypertension*, especially in the uncommon *familial form*, the TGF- $\beta$  signaling pathway. Specifically, germ-line mutations of *bone morphogenetic protein receptor 2* (*BMPR2*), a cell surface molecule that binds to a variety of TGF- $\beta$  pathway ligands, have been found in some cases. The *BMPR2* gene product is inhibitory in its effects on proliferation; hence, loss-of-function leads to abnormal vascular endothelial and pulmonary smooth muscle proliferation. The endothelial dysfunction is usually *monoclonal*, reiterating the genetic basis of their origin. Not all individuals with germ-line mutations have primary pulmonary hypertension, however, suggesting the existence of "*modifier genes*" that modify the particular phenotype. Studies on sporadic forms of primary pulmonary hypertension have identified a *serotonin transporter gene* (*5-HTT*). Specifically, pulmonary smooth muscle cells from some forms of hypertension demonstrate increased proliferation on exposure to serotonin or serum. Gene-environment interactions enhanced expression of the transporter protein on vascular smooth muscle are postulated. *5-HTT* function may also be the basis for pulmonary hypertension arising in persons taking tricyclic antidepressant derivatives.

### Morphology

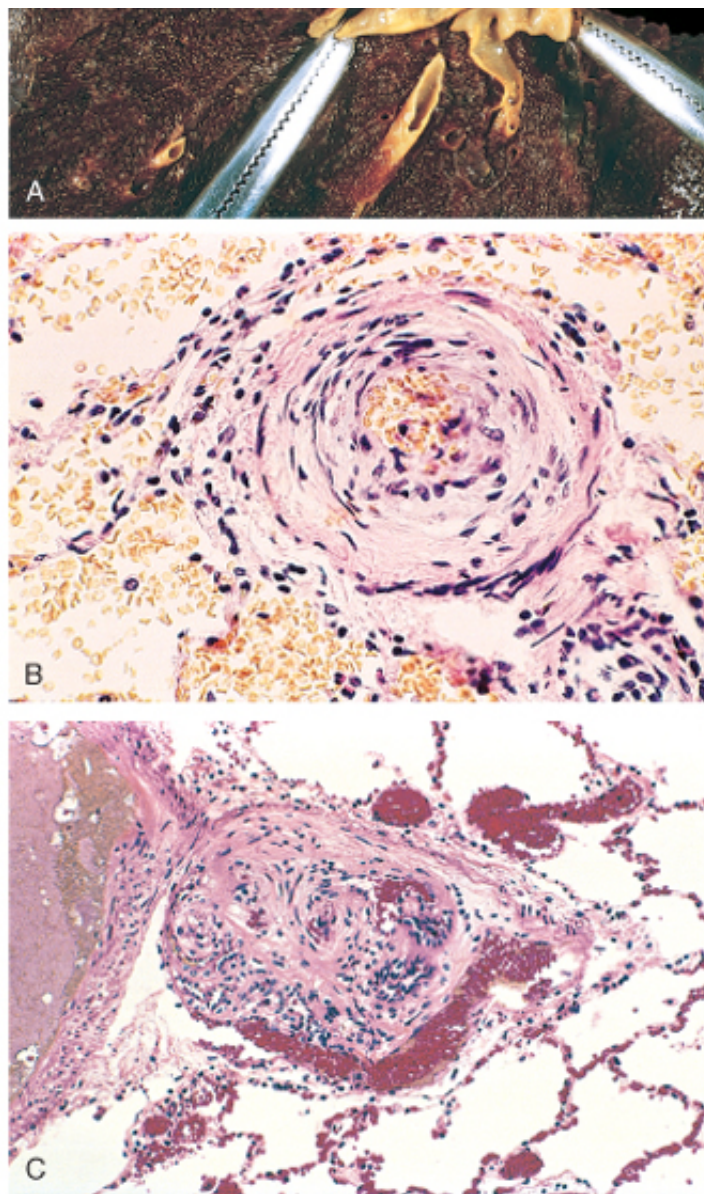
Vascular alterations in all forms of pulmonary hypertension (primary and secondary) are similar (Fig. 13-27) and include: (1) in the **main elastic arteries**, atherosclerotic changes similar to atherosclerosis; (2) in **medium-sized muscular arteries**, proliferation of myointimal smooth muscle cells, causing thickening of the intima and media with narrowing of the lumen; (3) in **arteries and arterioles**, thickening, medial hypertrophy, and reduplication of the internal elastic lamina. In these vessels, the wall thickness may exceed the diameter of the lumen, narrowing to the point of near-oblivation. Individuals with severe, long-standing primary pulmonary hypertension may develop **plexogenic pulmonary arteriopathy**, so called because of the complex, web-like formations that are present, producing a network, or web, that spans the lumens of dilated arteries.

### Clinical Course

Secondary pulmonary hypertension may develop at any age. The clinical features reflect the underlying cardiac disease, with accentuation of respiratory insufficiency and right-sided heart strain. Primary pulmonary hypertension is almost always encountered in young persons, more commonly women, and is marked by fatigue, dyspnea on exertion, and sometimes chest pain. These persons eventually develop severe respiratory failure. Death usually results from right-sided heart failure (decompensated cor pulmonale) within 2 to 5 years. In some cases, relief of the respiratory distress can be achieved by vasodilators and antithrombotic agents, but without long-term benefit.

### Diffuse Alveolar Hemorrhage Syndromes





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Figure 13-27 Vascular changes in pulmonary hypertension. **A**, Gross photograph of atheroma formation, a finding in pulmonary hypertension. **B**, Intimal hyperplasia. **C**, Plexogenic lesion characteristic of advanced pulmonary hypertension.

While there may be several "secondary" causes of pulmonary hemorrhage (necrotizing bacterial pneumonia, coagulopathy, or bleeding diathesis), the diffuse alveolar hemorrhage syndromes are a group of "primary" immune-mediated disorders characterized by a *triad of hemoptysis, anemia, and diffuse pulmonary infiltrates*.

### **Goodpasture Syndrome**

Goodpasture syndrome, the prototype disorder of this group, is an uncommon but intriguing condition characterized by *usually rapidly progressive, glomerulonephritis (Chapter 14)* and *hemorrhagic interstitial pneumonia*. Lesions are caused by antibodies targeted against the noncollagenous domain of the  $\alpha 3$  chain of type IV collagen, which is detected in the serum of more than 90% of persons with Goodpasture syndrome.

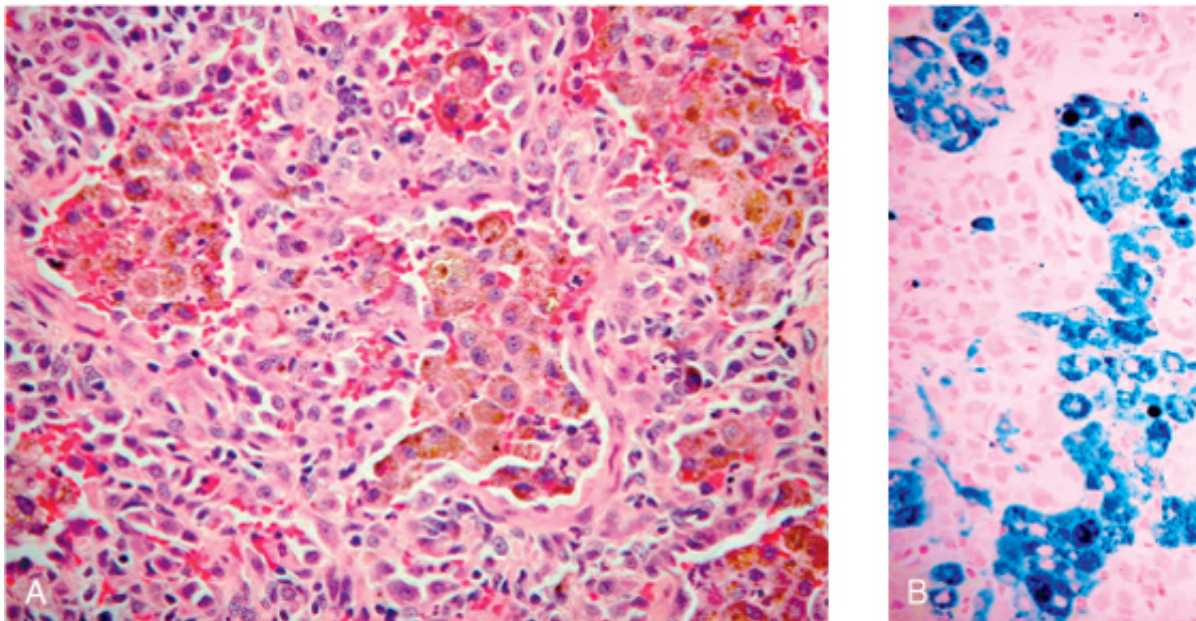
### **Morphology**

In the classic case of **diffuse alveolar hemorrhage**, the lungs are heavy, with areas of consolidation. Microscopic examination of the lungs demonstrates focal necrosis of

consolidation. Microscopic examination of the lungs demonstrates focal necrosis of alveolar walls with intra-alveolar hemorrhages, fibrous thickening of the septa, and hypertrophy of alveolar cells. The presence of **hemosiderin**, either within macrophages or extracellularly, is characteristic of the disease. The immunopathogenesis of Goodpasture syndrome changes in the glomeruli are discussed in [Chapter 14](#). Suffice it to say here that the **pattern of immunoglobulin deposition** (usually IgG, sometimes IgA or IgM) that is diagnostic in renal biopsy specimens is also seen along the alveolar septa.

Plasmapheresis and immunosuppressive therapy have markedly improved the once dismal prognosis of Goodpasture syndrome. Plasmapheresis removes offending antibodies, and immunosuppressive drugs inhibit antibody production. With these treatments, long-term survival is eventually required.

### ***Idiopathic Pulmonary Hemosiderosis***



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Figure 13-28 **A**, Lung biopsy specimen from a person with a diffuse alveolar hemorrhage syndrome demonstrates numerous macrophages on a background of thickened fibrous septa. **B**, The tissue has been stained with Prussian blue, an iron stain, highlighting the macrophages containing hemosiderin. (From the teaching collection of the Department of Pathology, Children's Medical Center, Denver, Colorado.)

Idiopathic pulmonary hemosiderosis is a disease of uncertain etiology that has pulmonary manifestations similar to Goodpasture syndrome, but there is no associated renal disease or circulating anti-basement membrane antibodies. The disease is usually mild to moderate, with periods of activity followed by prolonged, often spontaneous, remission, although the disease is reported in adults as well.

### ***Pulmonary Angiitis and Granulomatosis (Wegener Granulomatosis)***

Wegener granulomatosis (WG) is the prototype of the group of vasculitides known as pulmonary vasculitis, discussed in [Chapter 10](#). In this section we will focus on the manifestations of WG in the respiratory tract. Patients with WG develop upper respiratory or pulmonary manifestations at some time in the course of the disease. The disease is characterized by a combination of necrotizing vasculitis ("angiitis") and parenchymal necrotizing granulomatous inflammation. Pulmonary vessels may also show necrotizing granulomas, although most often acute and chronic fibrinoid necrosis. The manifestations of WG can include both upper respiratory symptoms (chronic sinusitis) and pulmonary symptoms (cough, hemoptysis, chest pain). Radiologically, multiple nodular densities and cavitary lesions are seen, some of which may undergo cavitation. Although WG is classically restricted to the lung without upper respiratory tract or renal involvement ("limited" WG).









## PULMONARY INFECTIONS

Pulmonary infections in the form of pneumonia are responsible for one-sixth of all deaths in the US because (1) the epithelial surfaces of the lung are constantly exposed to liters of variously contaminated air; (2) the lung is a common site for the entry of virulent organisms; and (3) other common lung diseases reduce the effectiveness of pulmonary defense mechanisms. It is therefore a small miracle that the normal lung parenchyma remains sterile despite the constant onslaught of pulmonary defense mechanisms. A plethora of immune and nonimmune defense mechanisms, extending from the nasopharynx all the way into the alveolar airspaces (Table 13-6, Fig. 13-29). The constant infectious onslaught.

Despite the multitude of defense mechanisms, "chinks in the armor" do exist, and they predispose to infections with pyogenic bacteria. On the other hand, cell-mediated immune defects lead to increased susceptibility to infections such as mycobacteria and herpesviruses as well as with microorganisms of very low virulence such as *Pneumocystis carinii*. Exogenous aspects of lifestyle interfere with host immune defense mechanisms and facilitate infection. Smoking compromises mucociliary clearance and pulmonary macrophage activity, while alcohol not only impairs host defenses thereby increasing the risk of aspiration, but also interferes with neutrophil mobilization and chemotaxis.

**Table 13-6. Pulmonary Host Defenses**

Location	Host Defense Mechanism
<b>Upper Airways</b>	
Nasopharynx	Nasal hair
	Turbinates
	Mucociliary apparatus
	Immunoglobulin A (IgA) secretion
Oropharynx	Saliva
	Sloughing of epithelial cells
	Local complement production
	Interference from resident flora
<b>Conducting Airways</b>	
Trachea, bronchi	Cough, epiglottic reflexes
	Sharp-angled branching of airways
	Mucociliary apparatus
	Immunoglobulin production (IgG, IgM, IgA)
<b>Lower Respiratory Tract</b>	
Terminal airways, alveoli	Alveolar lining fluid (surfactant, Ig, complement, fibronectin)
	Cytokines (interleukin 1, tumor necrosis factor)
	Alveolar macrophages
	Polymorphonuclear leukocytes
	Cell-mediated immunity

Reproduced from Mandell GL, et al. (eds): Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases, 5th ed. Philadelphia, PA: Elsevier; 2005.

*Pneumonia can be very broadly defined as any infection in the lung.* It may present as acute, fulminant disease with a more protracted course. The histologic spectrum of pneumonia may vary from a fibrin exudate in acute bacterial pneumonias, to mononuclear interstitial infiltrates in viral and other atypical pneumonias. In many of the chronic pneumonias. Acute bacterial pneumonias can present as one of two anatomic patterns: bronchopneumonia and lobar pneumonia. Bronchopneumonia implies a patchy distribution of infection, while lobar pneumonia implies a more uniform distribution of infection throughout a lobe of the lung.

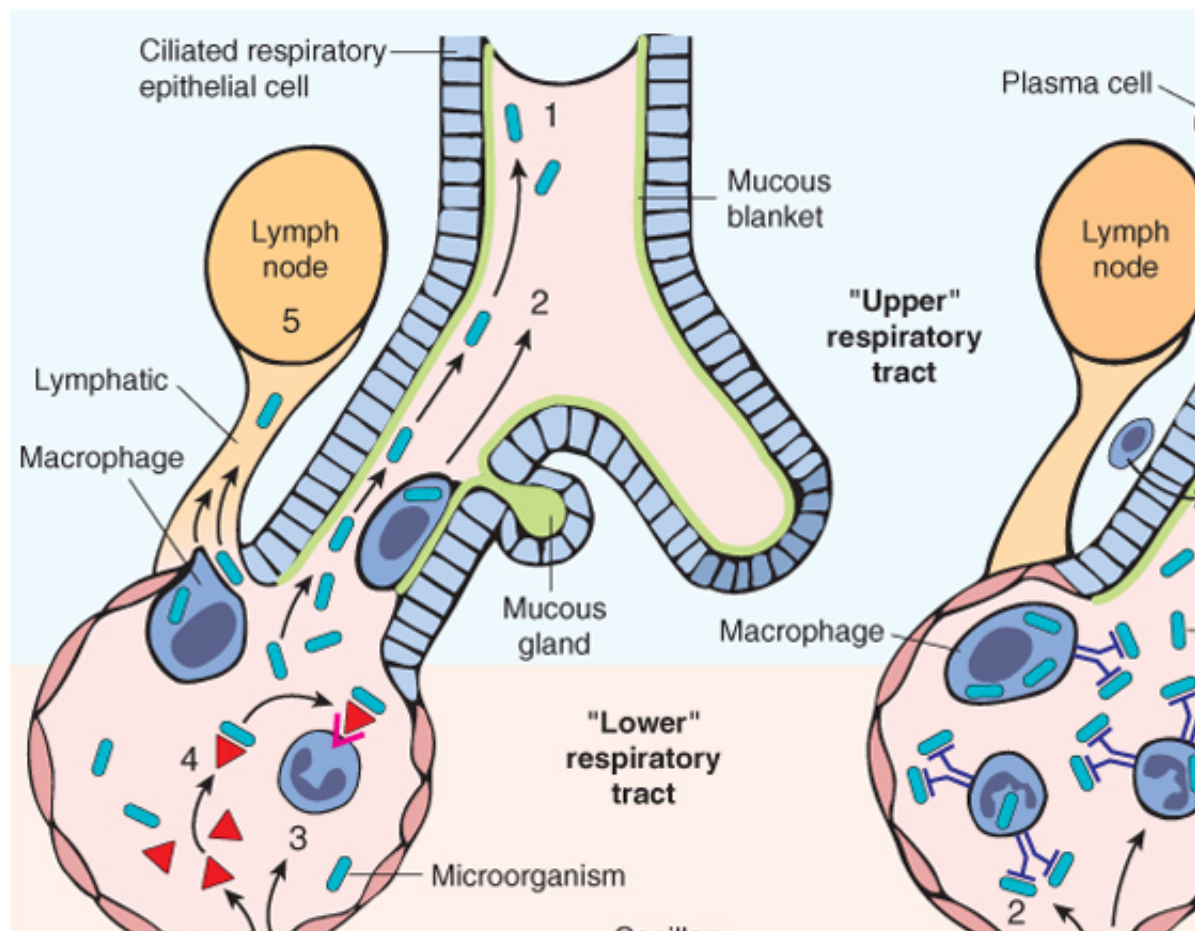
as bronchopneumonia and lobar pneumonia. Bronchopneumonia implies a patchy distribution of infection involving more than one lobe (Fig. 13-30). This pattern results from an initial infection of the bronchi and bronchial alveoli. By contrast, in lobar pneumonia the contiguous airspaces of part or all of a lobe are homogeneously consolidated and can be visualized on radiographs as a lobar or segmental consolidation (see Fig. 13-30). *Streptococcus pneumoniae* causes more than 90% of lobar pneumonias. The anatomic distinction between lobar pneumonia and bronchopneumonia is difficult because (1) many organisms present with either of the two patterns of distribution and (2) confluent bronchopneumonia can distinguish radiologically from lobar pneumonia. Therefore, it is best to classify pneumonias either by the pathogen that can be isolated, or by the clinical setting in which infection occurs. Classifying pneumonias in this way considerably narrows the list of suspected pathogens for administering empirical antimicrobial therapy. The pneumonia can arise in seven distinct clinical settings ("pneumonia syndromes"), and the implications for each category.

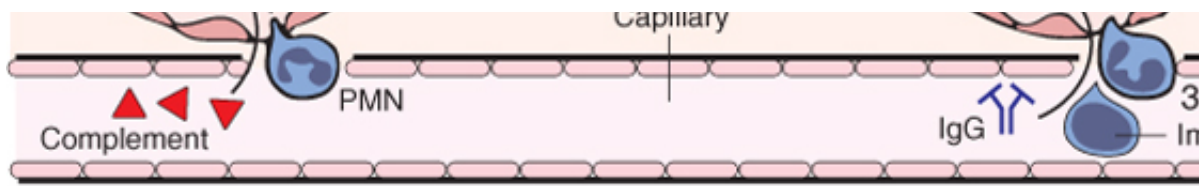
### Community-Acquired Acute Pneumonias

Most community-acquired acute pneumonias are bacterial in origin. Not uncommonly, the infection is viral. The onset is usually abrupt, with high fever, shaking chills, pleuritic chest pain, and a productive cough. Some patients may have hemoptysis. *S. pneumoniae* (or *pneumococcus*) is the most common cause of community-acquired pneumonia. Hence, pneumococcal pneumonia will be discussed as the prototype for this subgroup.

#### *Streptococcus pneumoniae*

*Pneumococcal* infections occur with increased frequency in three groups of individuals: (1) those with chronic heart failure (CHF), COPD, or diabetes; (2) those with either congenital or acquired immunoglobulin defects (e.g., agammaglobulinemia); and (3) those with decreased or absent splenic function (e.g., sickle cell disease or asplenia). Because the spleen contains the largest collection of phagocytes and is, therefore, the major organ for removing bacteria from the blood.



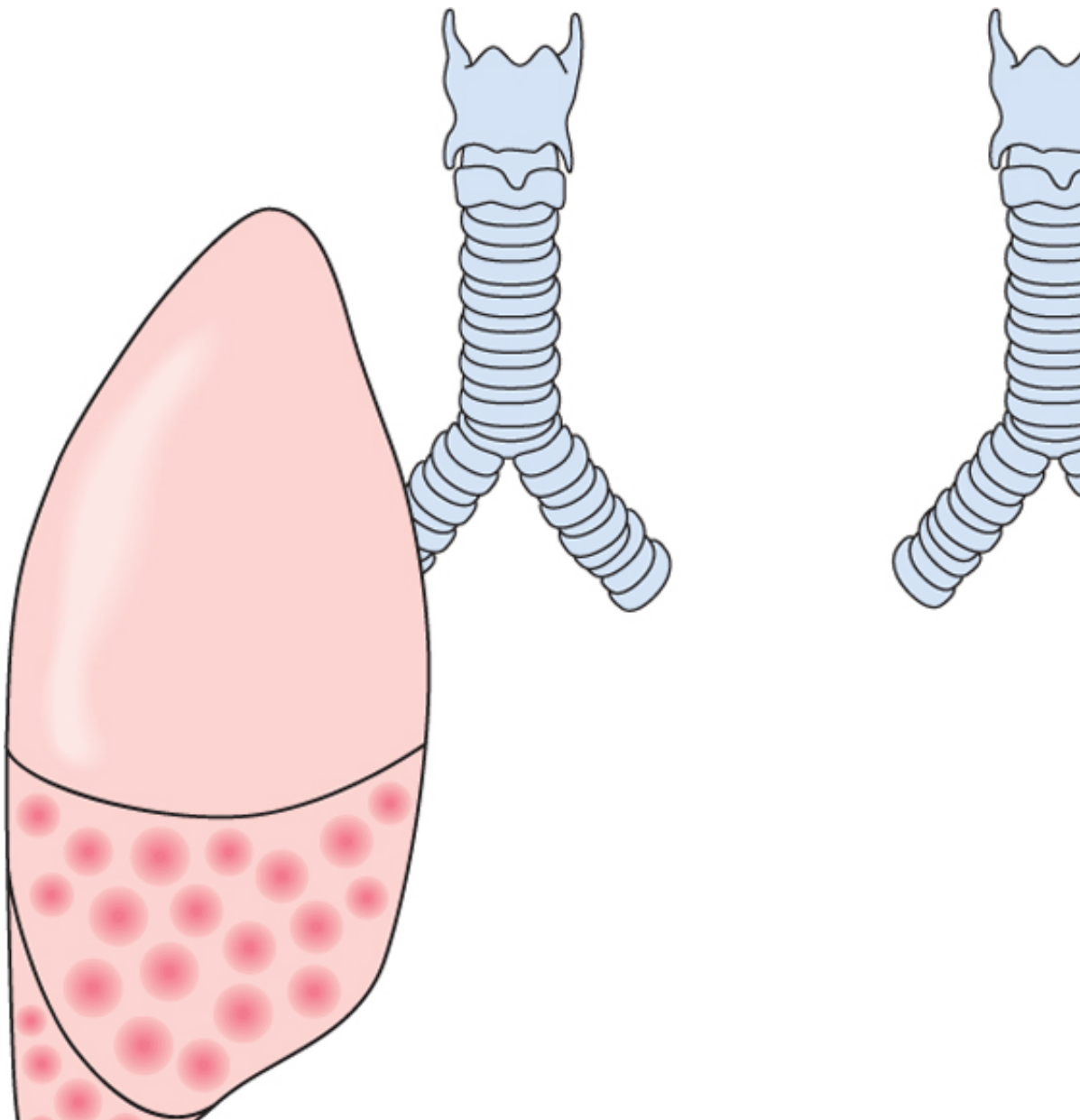


#### A. INNATE IMMUNE DEFENSES

#### B. ADAPTIVE

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Figure 13-29 Lung defense mechanisms. **A**, (1) In the nonimmune lung, removal of microbial organisms depends on the mucociliary elevator, (2) phagocytosis by alveolar macrophages that can kill and degrade organisms and return them to the mucociliary elevator, or (3) phagocytosis and killing by neutrophils recruited by macrophage factors. (4) Serum activated by the alternative pathway to provide the opsonin C3b that enhances phagocytosis. (5) Organisms, including bacteria, are removed from the lung by draining lymph nodes to initiate immune responses. **B**, Additional mechanisms operate after development of an adaptive immune response. (1) In the upper respiratory tract, antibodies (IgG) bind to microorganisms, enhancing their removal by the mucociliary elevator. (2) In the lower respiratory tract, serum lining fluid. They activate complement more efficiently by the classic pathway, yielding C3b (not shown). In addition, T cells are important for controlling infections by viruses and other intracellular microorganisms. P





# Bronchopneumonia

# Lobar

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Figure 13-30 The anatomic distribution of bronchopneumonia and lobar pn

## Morphology

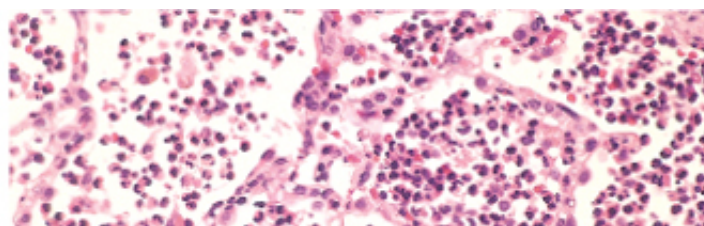
With pneumococcal lung infection, either pattern of pneumonia, lobar or bronchopn latter is much more prevalent at the extremes of age. Regardless of the distributio because pneumococcal lung infections usually originate by aspiration of pharynge harbor *S. pneumoniae* in their throats), the lower lobes or the right middle lobe are

In the era before antibiotics, pneumococcal pneumonia involved entire or almost ei through four stages: **congestion**, **red hepatization**, **gray hepatization**, and **resol therapy alters or halts this typical progression**, so if the person dies, the anatomic c may not conform to the classic stages.

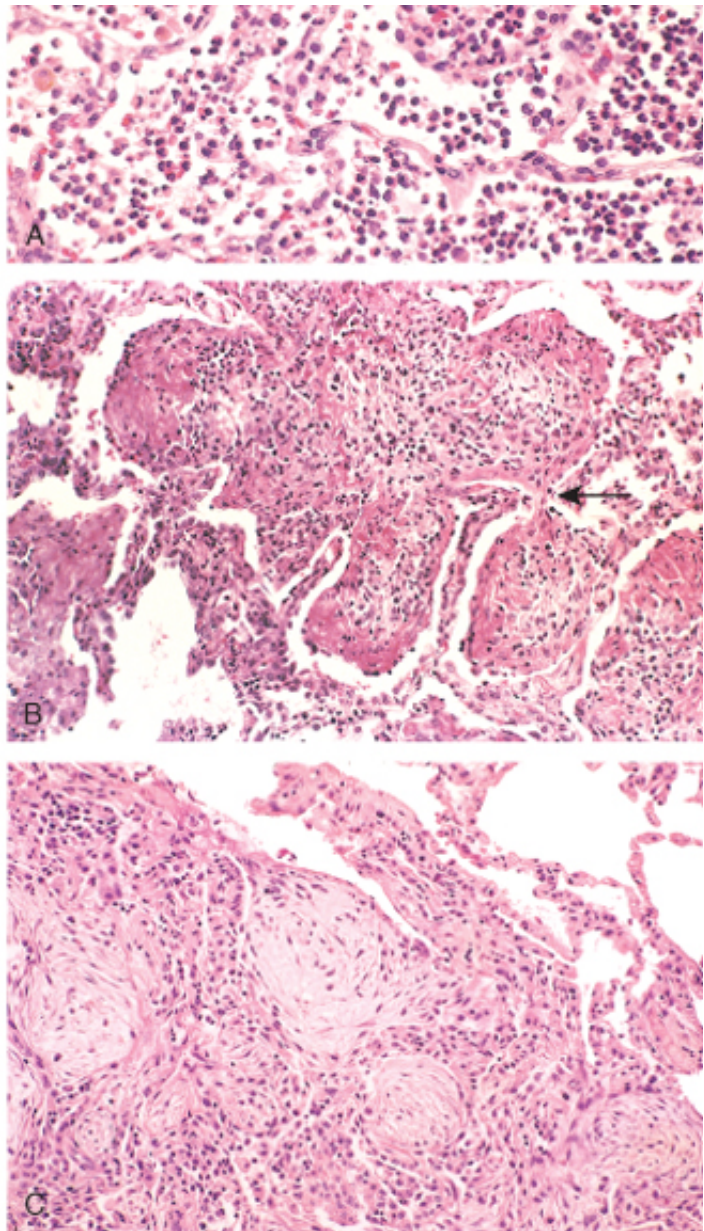
During the first stage, that of **congestion**, the affected lobe(s) is (are) heavy, red, & vascular congestion can be seen, with proteinaceous fluid, scattered neutrophils, a alveoli. Within a few days, the stage of **red hepatization** ensues, in which the lung consistency; the alveolar spaces are packed with neutrophils, red cells, and fibrin ( stage, **gray hepatization**, the lung is dry, gray, and firm, because the red cells are fibrinosuppurative exudate persists within the alveoli (Figs. 13-31B and 13-32). **Re: uncomplicated cases**, as exudates within the alveoli are enzymatically digested to semifluid debris that is resorbed, ingested by macrophages, coughed up, or organi into it (Fig. 13-31C). The pleural reaction (fibrinous or fibrinopurulent **pleuritis**) may undergo organization, leaving fibrous thickening or permanent adhesions.

In the **bronchopneumonic** pattern, foci of inflammatory consolidation are distribut one or several lobes, most frequently bilateral and basal. Well-developed lesions u are slightly elevated and are gray-red to yellow; confluence of these foci may occur producing the appearance of a lobar consolidation. The lung substance immediate consolidation is usually hyperemic and edematous, but the large intervening areas Pleural involvement is less common than in lobar pneumonia. Histologically, the re suppurative exudate that fills the bronchi, bronchioles, and adjacent alveolar space

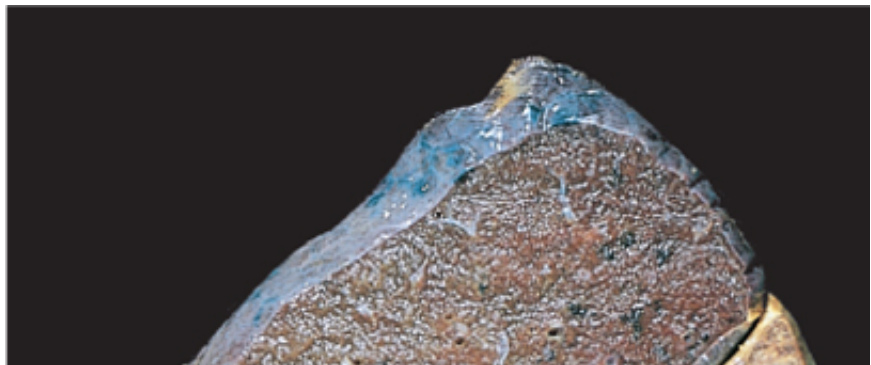
With appropriate therapy, complete restitution of the lung is the rule for both forms pneumonia, but in occasional cases complications may occur: (1) tissue destructio **abscess** formation; (2) suppurative material may accumulate in the pleural cavity, (3) organization of the intra-alveolar exudate may convert areas of the lung into sol bacteremic dissemination may lead to **meningitis**, **arthritis**, or **infective endocar much more likely with serotype 3 pneumococci.**

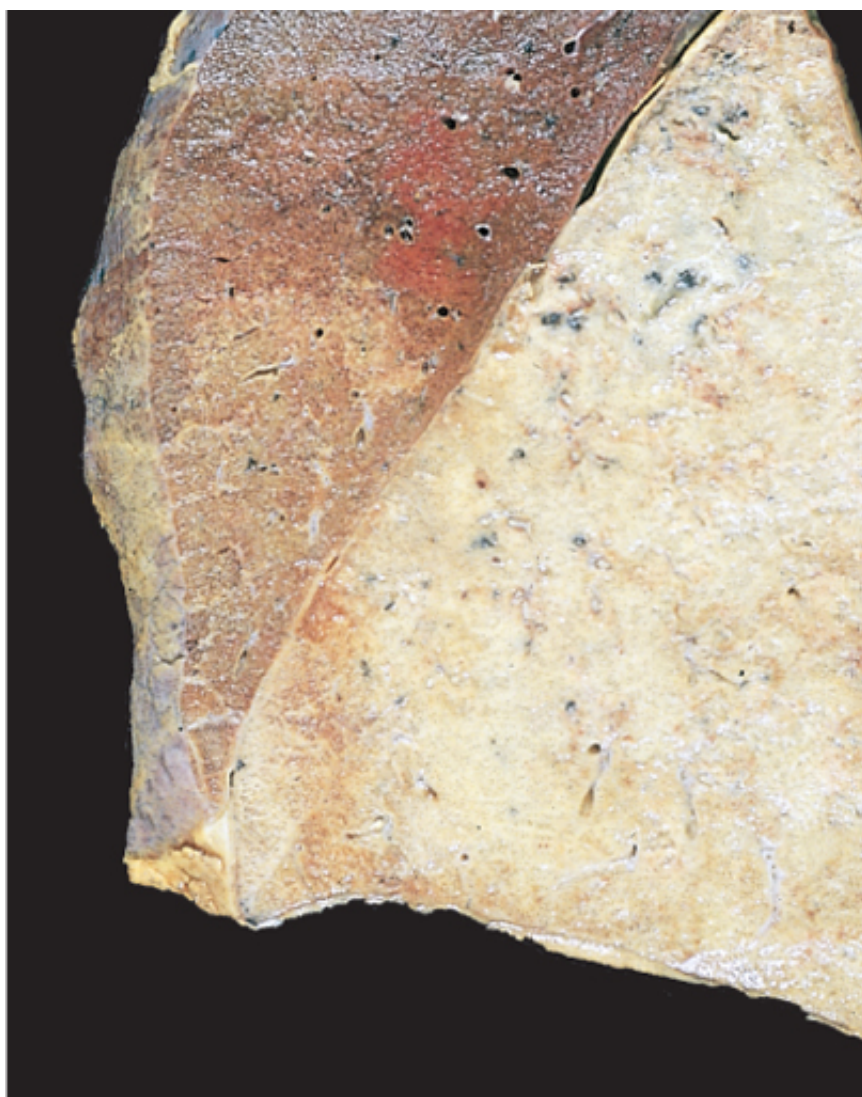






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 Figure 13-31 **A**, Acute pneumonia. The congested septal capillaries and extensive neutrophil exudation into alveoli have not yet formed. **B**, Early organization of intra-alveolar exudates, seen in areas to be streaming through the septa. **C**, Late organization of pneumonia, featuring transformation of exudates to fibromyxoid masses richly infiltrated by mononuclear cells.





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Figure 13-32 Gross view of lobar pneumonia with gray hepatization. The lower lobe is u

**Table 13-7. The Pneumonia Syndromes**

<b>Community-Acquired Acute Pneumonia</b>
<i>Streptococcus pneumoniae</i>
<i>Haemophilus influenzae</i>
<i>Moraxella catarrhalis</i>
<i>Staphylococcus aureus</i>
<i>Legionella pneumophila</i>
Enterobacteriaceae ( <i>Klebsiella pneumoniae</i> ) and <i>Pseudomonas</i> spp.
<b>Community-Acquired Atypical Pneumonia</b>
<i>Mycoplasma pneumoniae</i>
<i>Chlamydia</i> spp. ( <i>C. pneumoniae</i> , <i>C. psittaci</i> , <i>C. trachomatis</i> )
<i>Coxiella burnetii</i> (Q fever)
Viruses: respiratory syncytial virus, parainfluenza virus (children); influenza A and B (adults); adenovirus (r
<b>Nosocomial Pneumonia</b>
Gram-negative rods belonging to Enterobacteriaceae ( <i>Klebsiella</i> spp., <i>Serratia marcescens</i> , <i>Escherichia c</i>

Gram-negative rods belonging to Enterobacteriaceae (*Proteus* spp., *Serratia marcescens*, *Escherichia coli* (usually methicillin-resistant))

#### Aspiration Pneumonia

Anaerobic oral flora (*Bacteroides*, *Prevotella*, *Fusobacterium*, *Peptostreptococcus*), admixed with aerobic bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*)

#### Chronic Pneumonia

*Nocardia*

*Actinomyces*

Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum*, *Coccidioides immitis*

#### Necrotizing Pneumonia and Lung Abscess

Anaerobic bacteria (extremely common), with or without mixed aerobic infection *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae* (uncommon)

#### Pneumonia in the Immunocompromised Host

Cytomegalovirus

*Pneumocystis jirovecii*

*Mycobacterium avium-intracellulare*

Invasive aspergillosis

Invasive candidiasis

"Usual" bacterial, viral, and fungal organisms (listed above)

Examination of Gram-stained sputum is an important step in the diagnosis of acute pneumonia. The presence of Gram-positive diplococci is good evidence of pneumococcal pneumonia. The presence of Gram-negative diplococci is good evidence of *N. meningitidis*. The presence of Gram-negative bacilli is good evidence of *S. pneumoniae* is a part of the endogenous flora and therefore false-positive results may be caused by contamination. The presence of Gram-negative bacilli from blood cultures is more specific. During early phases of illness, blood cultures may be negative. Whenever possible antibiotic sensitivity should be determined. Commercial pneumococcal polysaccharides from the common serotypes of the bacteria are available, and their proven efficacy in the treatment of pneumococcal infections (see above).

Other organisms commonly implicated in community-acquired acute pneumonias include the following:

***Haemophilus influenzae*** Both *encapsulated* and *unencapsulated* forms are important causes of pneumonia. The former can cause a particularly life-threatening form of pneumonia in children, often fatal. Risk factors for developing infections include those with chronic pulmonary diseases such as chronic obstructive pulmonary disease and bronchiectasis. *H. influenzae* is the most common bacterial cause of acute exacerbation of COPD. *H. influenzae* was formerly an important cause of epiglottitis and suppurative meningitis in children, although the use of conjugate vaccine in infancy has significantly reduced the risk.

***Moraxella catarrhalis*** *M. catarrhalis* is being increasingly recognized as a cause of bacterial pneumonia. It is the second most common bacterial cause of acute exacerbation of COPD in adults. Along with *S. pneumoniae* and *H. influenzae*, *M. catarrhalis* constitutes one of the three most common causes of otitis media (infection of the middle ear).

***Staphylococcus aureus*** *S. aureus* is an important cause of secondary bacterial pneumonia following viral respiratory illnesses (e.g., measles in children and influenza in both children and adults). It is associated with a high incidence of complications, such as lung abscess and empyema. Staphylococcal pneumonia with right-sided staphylococcal endocarditis is a serious complication of *intravenous drug abuse* and is a cause of nosocomial pneumonia (see below).

***Klebsiella pneumoniae*** *K. pneumoniae* is the most frequent cause of gram-negative bacterial pneumonia in debilitated and malnourished persons, particularly *chronic alcoholics*. Thick and gelatinous capsules are characteristic. The organism produces an abundant viscid capsular polysaccharide, which the individual may have difficulty coughing up.

***Pseudomonas aeruginosa*** Although discussed here with community-acquired pathogens, *P. aeruginosa* is most commonly seen in nosocomial settings (see below). It is also common in persons who are neutropenic, usually secondary to chemotherapy; in victims of trauma; and in patients with chronic obstructive pulmonary disease.



mechanical ventilation. *P. aeruginosa* has a propensity to invade blood vessels at the site of extrapulmonary spread; *Pseudomonas* bacteremia is a fulminant disease, with death often days. Histologic examination reveals coagulation necrosis of the pulmonary parenchyma with necrotic blood vessels (*Pseudomonas* vasculitis).

***Legionella pneumophila*** *L. pneumophila* is the agent of legionnaire disease, an eponym for pneumonia caused by this organism. Pontiac fever is a related self-limited upper respiratory infection caused by *L. pneumophila*, without pneumonic symptoms. *L. pneumophila* flourishes in artificial aquatic environments, such as cooling towers and within the tubing system of domestic (potable) water supplies. The mode of transmission is by inhalation of aerosolized organisms or aspiration of contaminated drinking water. *Legionella* infection often occurs in individuals with some predisposing condition such as cardiac, renal, immunologic, or hematologic disease. *Legionella* pneumonia can be quite severe, frequently requiring hospitalization. Individuals may have a fatality rate of 30% to 50%. Rapid diagnosis is facilitated by demonstration of the organism by immunofluorescence or by a positive fluorescent antibody test on sputum samples; culture remains the gold standard.

### Community-Acquired Atypical Pneumonias

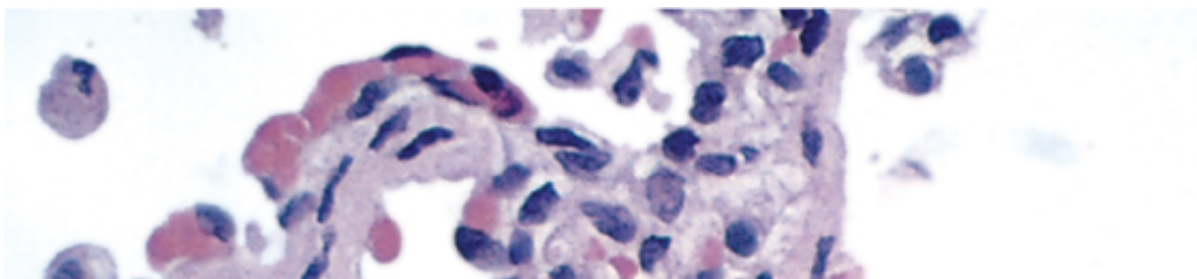
The term "primary atypical pneumonia" was initially applied to an acute febrile respiratory disease characterized by changes in the lungs, largely confined to the alveolar septa and pulmonary interstitium. The term is used because of the absence of sputum, absence of physical findings of consolidation, only moderate elevation of white cell count, and the absence of a clear-cut response to antibiotics. Atypical pneumonia is caused by a variety of organisms, *Mycoplasma pneumoniae* being the most common among children and young adults. They occur sporadically or as local epidemics (e.g., in military camps, prisons). Other etiologic agents are *viruses*, including influenza types A and B, the rhinoviruses, rubeola, and varicella viruses; *Chlamydia pneumoniae* and *Coxiella burnetii* (Q fever agent) can also cause a primarily upper respiratory tract infection ("common cold").

The common pathogenetic mechanism is attachment of the organisms to the respiratory epithelium, followed by an inflammatory response. When the process extends to alveoli there is usually *interstitial* inflammation, with outpouring of fluid into alveolar spaces so that on chest films the changes may mimic bacterial pneumonia. In the respiratory epithelium inhibits mucociliary clearance and predisposes to secondary bacterial infection. Lower respiratory tract infection is more likely in malnourished, alcoholics, and the immunosuppressed. Not surprisingly, viruses and mycoplasmas are common causes of infection in hospitals.

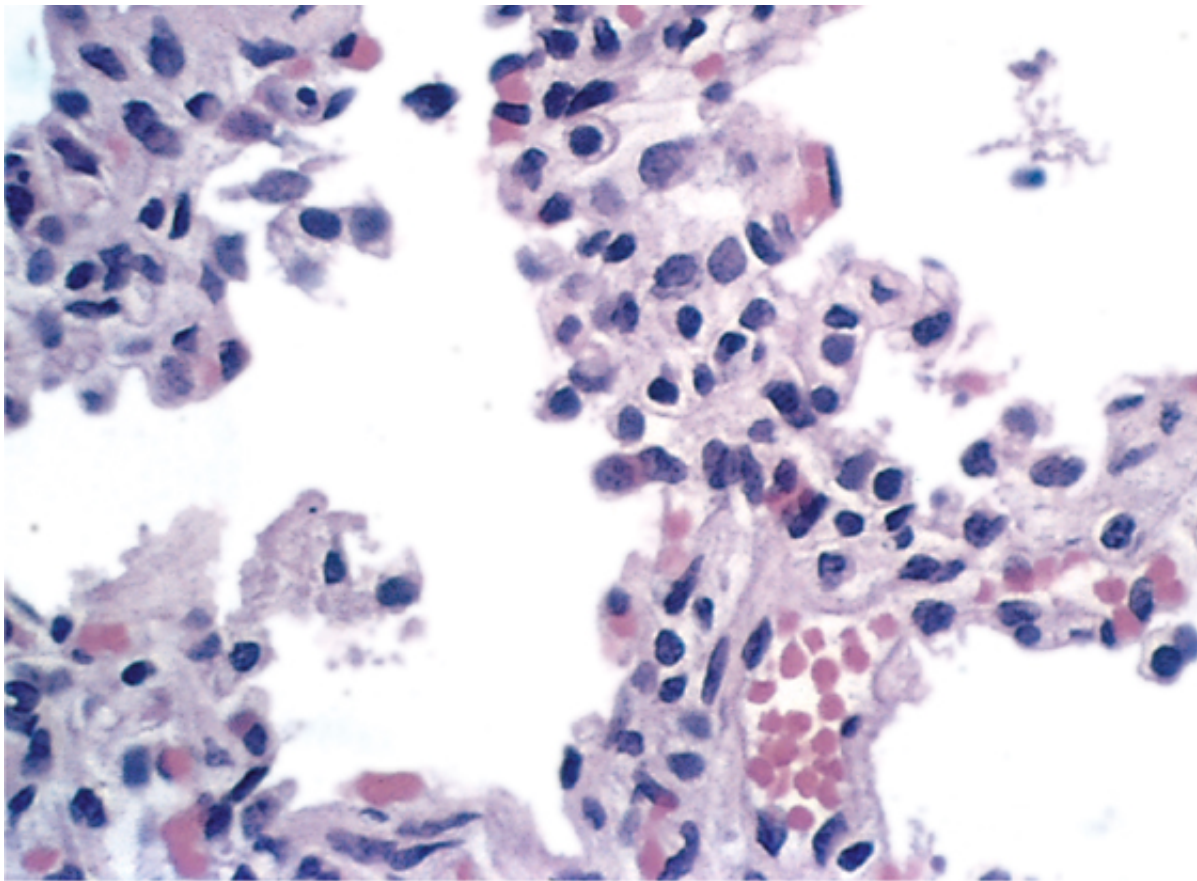
#### Morphology

Regardless of cause, the morphologic patterns in atypical pneumonias are similar. The process is patchy, or it may involve whole lobes bilaterally or unilaterally. Macroscopically, the lung is red, blue, congested, and subcrepitant. Histologically the **inflammatory reaction is largely confined to the walls of the alveoli** (Fig. 13-33). The septa are widened and edematous; they usually contain a mononuclear inflammatory infiltrate of lymphocytes, histiocytes, and, occasionally, plasma cells. In bacterial pneumonias, alveolar spaces in atypical pneumonias are remarkably free of exudate. In severe cases, however, full-blown diffuse alveolar damage with hyaline membrane formation occurs. In severe, uncomplicated cases, subsidence of the disease is followed by reconstitution of normal architecture. Superimposed bacterial infection, as expected, results in a mixed histologic picture.

#### Clinical Course







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Figure 13-33 Atypical pneumonia. The thickened alveolar walls are heavily infiltrated with i

The clinical course of primary atypical pneumonia is extremely varied. It may masquerade as a severe "chest cold" that goes undiagnosed, or it may present as a fulminant, life-threatening infection in infants. The clinical course is usually that of an acute, nonspecific febrile illness characterized by fever, headache, and malaise. Because the edema and exudation are both in a strategic position to cause an alveolocapillary block, the clinical picture is *seemingly out of proportion to the physical and radiographic findings*. Identifying the causative agent by immunofluorescence, enzyme immunoassay, and polymerase chain reaction (PCR) testing for *Mycoplasma* DNA are available. As a primary atypical pneumonia for which a bacterial agent seems unlikely are treated with a macrolide antibiotic. *Chlamydia pneumoniae*, because these are the most common treatable pathogens.

### **Influenza Infections**

Perhaps no other communicable disorder causes as much public distress in the developed world. The influenza virus is a single-stranded RNA virus, bound by a nucleoprotein that determines the shape of the virus. The surface of the virus is a lipid bilayer containing the viral hemagglutinin and neuraminidase, which (etc.). Host antibodies to the hemagglutinin and neuraminidase prevent and ameliorate, respectively, the effects of the virus. The type A viruses infect humans, pigs, horses, and birds and are the major cause of *pandemics*. Epidemics of influenza occur through mutations of the hemagglutinin and neuraminidase antigens to which the population has no preexisting antibodies (*antigenic drift*). Pandemics, which last longer and are more widespread than epidemics, occur when the hemagglutinin and neuraminidase are replaced through recombination of RNA segments with those of a previously susceptible virus (*antigenic shift*). Commercially available influenza vaccines are effective against the disease, especially in vulnerable infants and elderly individuals. A particular subtype of avian influenza virus caused massive outbreaks in domesticated poultry in parts of Southeast Asia in the last few years; this strain has the potential to "jump" to humans and thereby cause an unprecedented, worldwide influenza pandemic.

## Severe Acute Respiratory Syndrome (SARS)

The severe acute respiratory syndrome (SARS) first appeared in November 2002 in the Guangdong province of China. It spread to Hong Kong, Taiwan, Singapore, Vietnam, and Toronto, where large outbreaks also occurred in 2003, when the outbreak culminated, over 8,000 cases and 774 deaths had been ascribed to SARS. The cause of SARS is an undiscovered coronavirus (SARS-CoV). Nearly a third of upper respiratory tract infections are caused by the common cold virus, which differs in its ability to infect the lower respiratory tract and induce viremia. The SARS-CoV appears to have been transmitted through contact with wild masked palm civets that are eaten in China. Subsequent cases were spread through infected secretions, although some cases may have been contracted through fecal-oral transmission. Symptoms typically follow systemic manifestations, and include dry cough and dyspnea, but unlike the common cold, respiratory tract symptoms are rare. The lungs of patients dying of SARS usually demonstrate diffuse alveolar damage with giant cells. The unraveling of the cause of SARS, including complete sequencing of the SARS-CoV genome, and the issuance of a WHO "global alert" represents a triumph of molecular medicine and the collaborative scientific effort.

### SUMMARY

**Acute Pneumonias** *S. pneumoniae* (pneumococcus) is the most common cause of community-acquired acute pneumonia, and the distribution of inflammation is usually lobar. Other common causes of acute pneumonias in the community include *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* (both associated with acute exacerbations of COPD), *S. aureus* (in hospital-acquired respiratory infections), *K. pneumoniae* (observed in chronic alcoholics), *P. aeruginosa* (in individuals with cystic fibrosis, in burn patients and in neutropenics), and *L. pneumophila*, particularly in individuals who have undergone organ transplants. In contrast, *atypical pneumonias* are characterized by respiratory distress out of proportion to the radiologic signs, and inflammation that is predominantly confined to alveolar septa, leaving clear alveoli. The most common causes of atypical pneumonias include those caused by *Mycoplasma pneumoniae*, viruses, including influenza types A and B, *C. pneumoniae*, and *Legionella pneumophila*.

## Nosocomial Pneumonia

Nosocomial, or hospital-acquired, pneumonias are defined as pulmonary infections acquired in the hospital. Nosocomial pneumonia places an immense burden on the burgeoning costs of health care, besides its impact on patient outcome. Nosocomial infections are common in hospitalized persons with severe underlying disease, and those on antibiotic therapy. Those on mechanical ventilation represent a particularly high-risk group, and in this group the distinctive designation *ventilator-associated pneumonia* is used. Gram-negative rods (*Enterobacteriaceae*) are the most common isolates; unlike community-acquired pneumonias, *S. pneumoniae* is rarely isolated in nosocomial infections.

## Aspiration Pneumonia

Aspiration pneumonia occurs in markedly debilitated patients or those who aspirate gastric contents (e.g., after a stroke) or during repeated vomiting. These individuals have abnormal gag and swallowing reflexes. Aspiration pneumonia is partly chemical, resulting from the extremely irritating effects of the gastric acid, and partly infectious. It is assumed that anaerobic bacteria predominate, but recent studies implicate aerobes more commonly. Aspiration pneumonia is often necrotizing, pursues a fulminant clinical course, and is a frequent cause of death. In those who survive, abscess formation is a common complication.

## Lung Abscess

Lung abscess refers to a localized area of suppurative necrosis within the pulmonary parenchyma, often surrounded by large cavities. The term *necrotizing pneumonia* has been used for a similar process resulting in necrosis. Lung pneumonia often coexists or evolves into lung abscess, making this distinction somewhat arbitrary. Lung abscess is introduced into the lung by any of the following mechanisms:

Aspiration of infective material from oropharyngeal cavity or infected sinuses or tonsils, particularly in the setting of impaired gag and swallowing reflexes.

*Aspiration of infective material* from carious teeth or infected sinuses or tonsils, particularly coma, or alcoholic intoxication and in debilitated patients with depressed cough reflexes. As accompanied by infectious organisms from the oropharynx. As a complication of necrotizing caused by *S. aureus*, *Streptococcus pyogenes*, *K. pneumoniae*, *Pseudomonas* spp., and, in children, *Legionella pneumophila* infections and bronchiectasis may also lead to lung abscesses. *Bronchial obstruction*, particularly obstructing a bronchus or bronchiole. Impaired drainage, distal atelectasis, and aspiration contribute to the development of abscesses. An abscess may also form within an excavate cavity. *Septic embolism*, from septic thrombophlebitis or from infective endocarditis of the right side of the heart, may result from *hematogenous spread of bacteria* in disseminated pyogenic infection. This occurs in staphylococcal bacteremia and often results in multiple lung abscesses. *Anaerobic bacteria*, such as *Bacteroides* and *Fusobacterium* sometimes in vast numbers, and they are the exclusive isolates in one-third to two-thirds of lung abscesses. Anaerobes are commensals normally found in the oral cavity, principally species of *Prevotella*, *Peptostreptococcus*, and microaerophilic streptococci.

### Morphology

Abscesses vary in diameter from a few millimeters to large cavities of 5 to 6 cm. The size of abscesses depend on their mode of development. Pulmonary abscesses resulting from aspiration of infective material are much **more common on the right side** (more vertical airway) and most are single. On the right side, they tend to occur in the posterior segment of the upper lobe or apical segments of the lower lobe, because these locations reflect the probable location of the abscess when the patient is recumbent. Abscesses that develop in the course of pneumonia are commonly multiple, basal, and diffusely scattered. Septic emboli and abscesses arising from septic seeding are commonly multiple and may affect any region of the lungs.

As the focus of suppuration enlarges, it almost inevitably ruptures into airways. This may be partially drained, producing an air-fluid level on radiographic examination. Rupture into the pleural cavity and produce bronchopleural fistulas, the consequence is **pneumothorax or empyema**. Other complications arise from embolization of septic emboli giving rise to meningitis or brain abscess. Histologically, as expected with any abscess, it is surrounded by variable amounts of fibrous scarring and mononuclear infiltration (lymphocytes and macrophages), depending on the chronicity of the lesion.

### Clinical Course

The manifestations of a lung abscess are much like those of bronchiectasis and include a prominent cough with large amounts of foul-smelling, purulent, or sanguineous sputum; occasionally, hemoptysis occurs. Spontaneous Clubbing of the fingers, weight loss, and anemia may all occur. Infective abscesses occur in 10% of lung carcinoma; thus, when a lung abscess is suspected in an older person, underlying carcinoma must be ruled out (Chapter 5) may develop in chronic cases. Treatment includes antibiotic therapy and, if needed, surgery. The mortality rate is in the range of 10%.

### Chronic Pneumonia

Chronic pneumonia is most often a localized lesion in an immunocompetent person, with or without cavitation. There is typically granulomatous inflammation, which may be due to bacteria (e.g., *M. tuberculosis*), fungi, or parasites, such as those with debilitating illness, on immunosuppressive agents, or with human immune deficiency virus. In these cases, there is usually systemic dissemination of the causative organism, accompanied by widespread disease. Chronic pneumonia is an important entity within the spectrum of chronic pneumonias, with the World Health Organization (WHO) estimating that 6% of all deaths worldwide, making it the most common cause of death resulting from a single infectious agent.

### Tuberculosis

Tuberculosis is a communicable chronic granulomatous disease caused by *Mycobacterium tuberculosis*. It may affect any organ or tissue in the body. Typically, the centers of tubercular granulomas undergo caseation.

### Epidemiology

Among medically and economically deprived persons throughout the world, tuberculosis remains that 1.7 billion individuals are infected worldwide, with 8 to 10 million new cases and 3 million deaths from tuberculosis peaked in 1800 and steadily declined throughout the 1800s and 1900s. However, it stopped abruptly, a change that resulted from the increased incidence of tuberculosis in HIV-infected surveillance and tuberculosis prophylaxis among immunosuppressed individuals, the incidence of tuberculosis declined since 1992. Currently, it is estimated that about 25,000 new cases with active tuberculosis annually, nearly 40% of these are in immigrants from countries where tuberculosis is highly prevalent.

Tuberculosis flourishes wherever there is poverty, crowding, and chronic debilitating illness. Similar defenses, are vulnerable. In the United States, tuberculosis is a disease of the elderly, the urban poor, and belonging to minority communities. African Americans, Native Americans, the Inuit (from Alaska), and Southeast Asia have higher attack rates than other segments of the population. *Certain diseases* such as diabetes mellitus, Hodgkin disease, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, and immunosuppression. In areas of the world where HIV infection is prevalent, *it has become the sine qua non for the development of tuberculosis*. Most, perhaps all, of these predisposing conditions are related to a decreased ability to maintain T cell-mediated immunity against the infectious agent.

It is important that *infection* be differentiated from *disease*. Infection implies seeding of a focus without necessarily causing clinically significant tissue damage (i.e., disease). Although other routes may be involved, the primary route is person-to-person transmission of airborne droplets of organisms from an active case to a susceptible individual. An asymptomatic focus of pulmonary infection appears that is self-limited, although, uncommonly, prior to the development of fever and pleural effusion. Generally, the only evidence of infection, if any remains, is the site of the infection. Viable organisms may remain dormant in such loci for decades, and persons may be infected but do not have active disease and so cannot transmit organisms to others. Yet when conditions are favorable, they may reactivate to produce communicable and potentially life-threatening disease.

Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity, which is tested by the (Mantoux) test. About 2 to 4 weeks after the infection has begun, intracutaneous injection of 0.1 ml of purified protein derivative (PPD) produces an induration (at least 5 mm in diameter) that peaks in 48 to 72 hours. Sometimes, more PPD is required. Unfortunately, in some responders, the standard dose may produce a large, necrotizing lesion. A delayed-type hypersensitivity to tubercular antigens. It does not differentiate between infection and disease. *Negative reactions (or skin test anergy) may be produced by certain viral infections, sarcoidosis, renal failure, immunosuppression, and (notably) overwhelming active tuberculous disease*. False-positive reactions may be caused by atypical mycobacteria.

About 80% of the population in certain Asian and African countries is tuberculin positive. By contrast, in the United States, only about 10% of the population reacted positively to tuberculin, indicating the marked difference in rates of exposure to the organism. About 4% of previously unexposed individuals acquire active tuberculosis during the first year after "tuberculin conversion," and 15% do so thereafter. Thus, *only a small fraction of those who contract an infection develop active disease*.

### *Etiology*

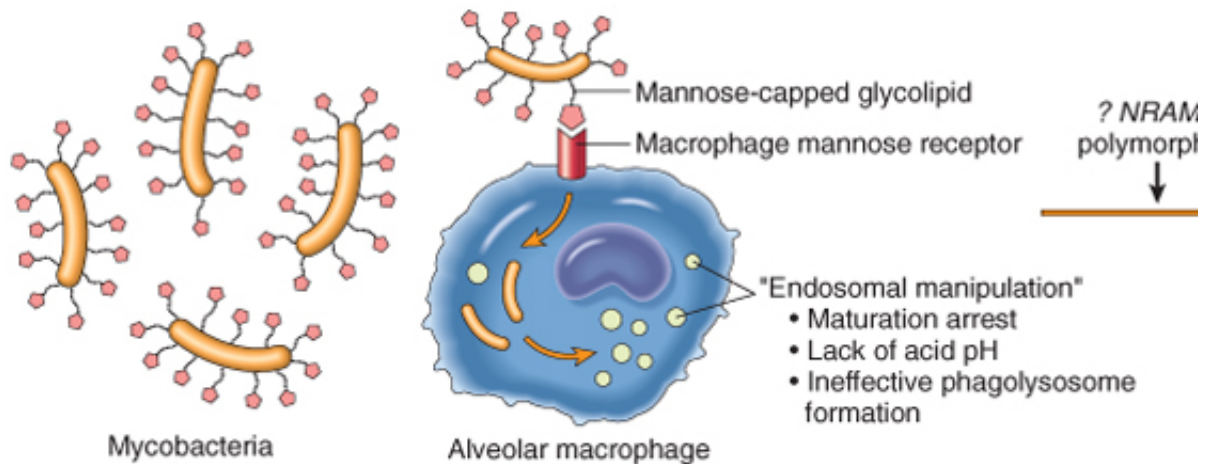
Mycobacteria are slender rods that are acid fast (i.e., they have a high content of complex lipids that resist decolorization by fuchsin stain and subsequently stubbornly resist decolorization). *M. tuberculosis hominis* is the most important reservoir of infection is usually found in humans with active pulmonary disease. Transmission is usually by aerosols generated by expectoration or by exposure to contaminated secretions of infected individuals. In children, intestinal tuberculosis contracted by drinking milk contaminated with *Mycobacterium bovis* is now rare. Both *M. tuberculosis* and *M. bovis* are aerobes whose slow growth is retarded by a pH lower than 6.5 and by long-chain fatty acids, hence they are found in the centers of large caseating lesions where anaerobiosis, low pH, and increased levels of fatty acids are present. Particularly *M. avium-intracellulare*, are much less virulent than *M. tuberculosis* and rarely cause disease. However, in patients with AIDS, these strains are frequently found, affecting 10% to 30% of patients.

### *Pathogenesis*

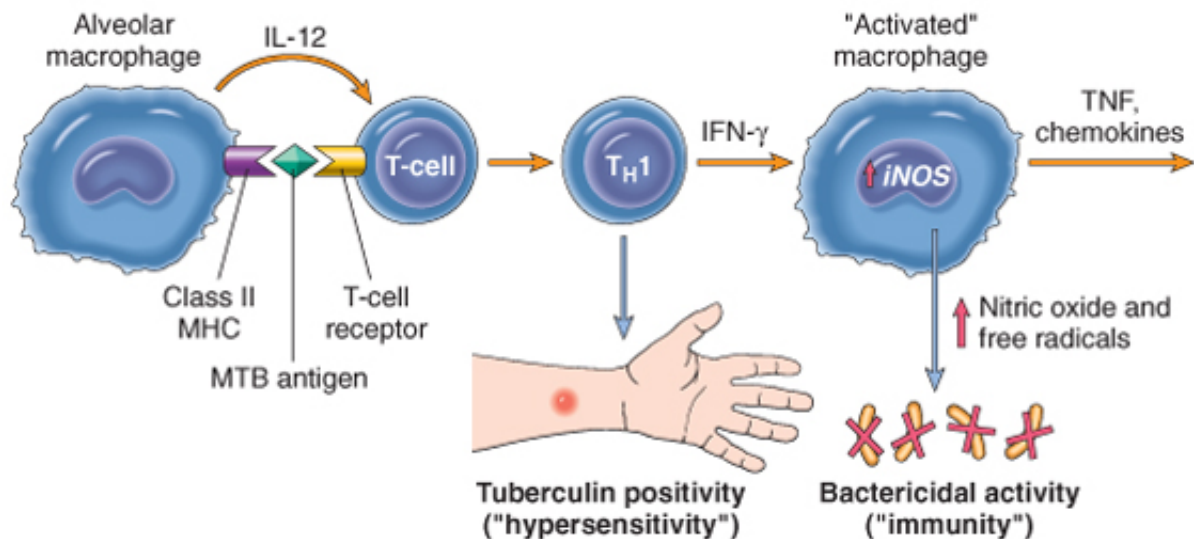
A. PRIMARY PULMONARY TUBERCULOSIS (A. P. P. T.)



#### A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)



#### B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)



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Figure 13-34 The sequence of events in primary pulmonary tuberculosis, commencing with inhalation of virulent *M. tuberculosis* and development of immunity and delayed hypersensitivity to the organism. **A**, Events occurring in the first 3 weeks of infection. **B**, Development of resistance to the organism is accompanied by the appearance of a positive tuberculin test. Cells: iNOS, inducible nitric oxide synthase; IFN- $\gamma$ , interferon  $\gamma$ ; MHC, major histocompatibility complex; MTB, *Mycobacterium tuberculosis* macrophage protein; TNF, tumor necrosis factor.

The pathogenesis of tuberculosis in the previously *unexposed immunocompetent* individual is cell-mediated immunity that confers *resistance* to the organism and results in development of *tissue* immunity. The pathologic features of tuberculosis, such as caseating granulomas and cavitation, are the result of *tissue* hypersensitivity that is part and parcel of the host immune response. Because the effector cells for the appearance of tissue hypersensitivity also signals the acquisition of immunity to the organism. The sequence of events from the infectious inoculum to containment of the primary focus is illustrated in Fig. 13-34A and B and

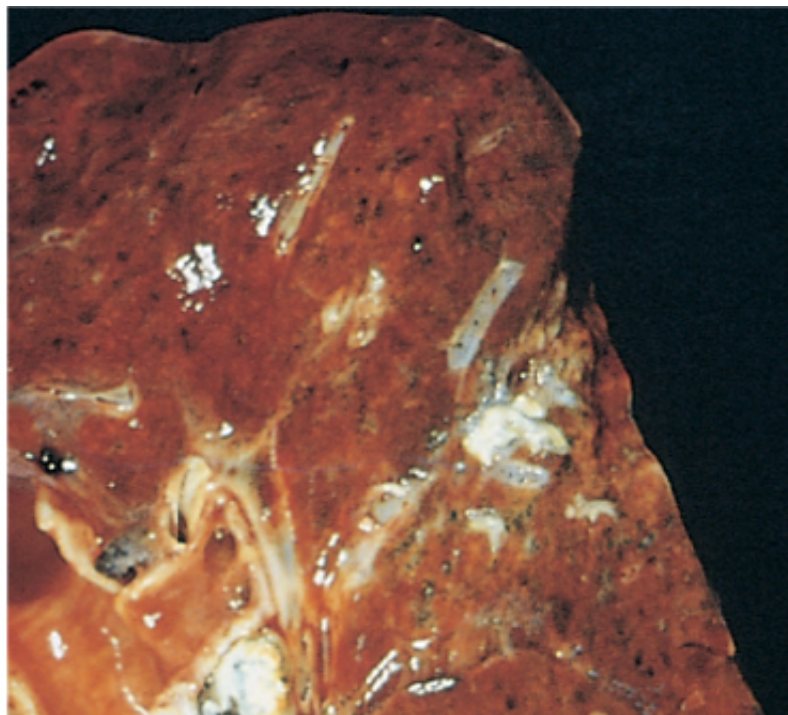
Once virulent strains of mycobacteria gain entry into the macrophage endosomes (a process that involves several receptors, including the macrophage mannose receptor and complement receptors that recognize mycobacterial cell walls), the organisms are able to inhibit normal microbicidal responses by

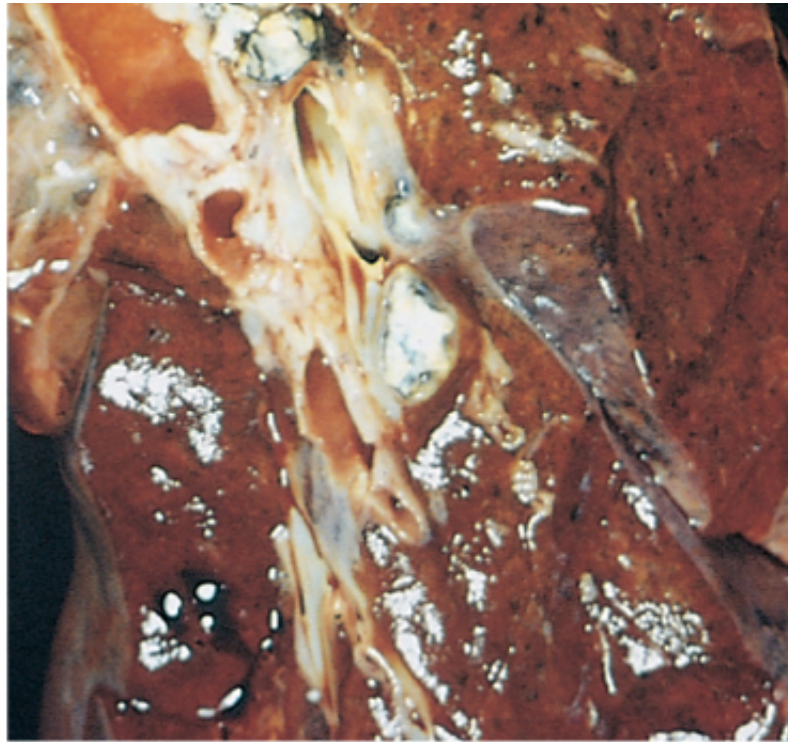
arrest of endosomal maturation. The end result of this "endosomal manipulation" is impaired formation and unhindered mycobacterial proliferation. Thus, the earliest phase of primary tuberculosis in a non-sensitized individual is characterized by bacillary proliferation within the pulmonary alveoli, resulting in bacteremia and seeding of multiple sites. *Despite the bacteremia, most persons develop a mild flu-like illness.* The genetic makeup of the individual may influence the course of the disease. Polymorphisms of the *NRAMP1* (natural resistance-associated macrophage protein 1) gene point to the development of an effective immune response. *NRAMP1* is a transmembrane protein found in endosomes and lysosomes that is believed to contribute to microbial killing. The development of granulomas occurs approximately 3 weeks after exposure. Processed mycobacterial antigens reach the draining lymph node in the context of major histocompatibility class II molecules and are presented to CD4<sup>+</sup> T cells. Upon exposure to IL-12, CD4<sup>+</sup> T cells of the T<sub>H</sub>1 subset are generated, capable of secreting IFN- $\gamma$ . *IFN- $\gamma$  release is crucial in activating macrophages.* Activated macrophages, in turn, release a variety of effector molecules, including (a) secretion of TNF, which is responsible for recruitment of monocytes and differentiation into the "epithelioid histiocytes" that characterize the granulomatous response; (b) *nitric oxide synthase (iNOS)* gene, which results in elevated *nitric oxide* levels at the site of infection, acting as an oxidizing agent and resulting in generation of reactive nitrogen intermediates and other free radicals; (c) generation of reactive oxygen species. Defects in any of the steps of a T<sub>H</sub>1 response (including IL-12, IFN- $\gamma$ , TNF, or *nitric oxide*) can lead to the formation of granulomas, absence of resistance, and disease progression.

*In summary, immunity to a tubercular infection is primarily mediated by T<sub>H</sub>1 cells, which stimulate an immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue damage. The infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of immune cells, leading to increased tissue necrosis. Just as hypersensitivity and resistance appear in parallel, so, too, the loss of resistance (tuberculin negativity in a tuberculin-positive individual) may be an ominous sign that resistance to tuberculosis is waning.*

### Primary Tuberculosis

*Primary tuberculosis is the form of disease that develops in a previously unexposed, and therefore susceptible, individual. In immunocompetent persons, the disease is usually self-limiting and resolves within a few weeks. However, in immunosuppressed persons, the disease may be more severe and persistent. With primary tuberculosis, the source of the organism is exogenous. About 5% of infected persons develop disease.*



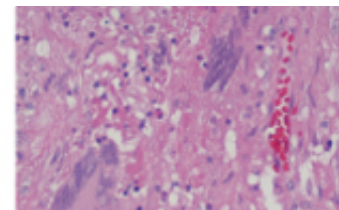
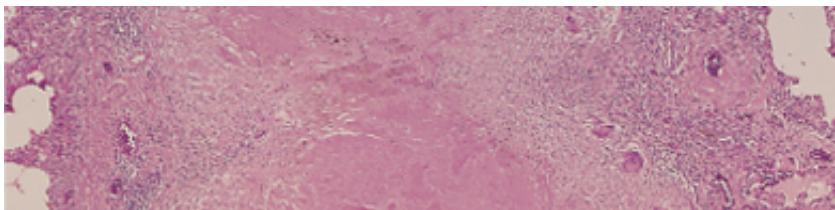


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 Figure 13-35 Primary pulmonary tuberculosis, Ghon complex. The gray-white parenchymal focus is under the pleura. Regional lymph nodes with caseation are seen on the left.

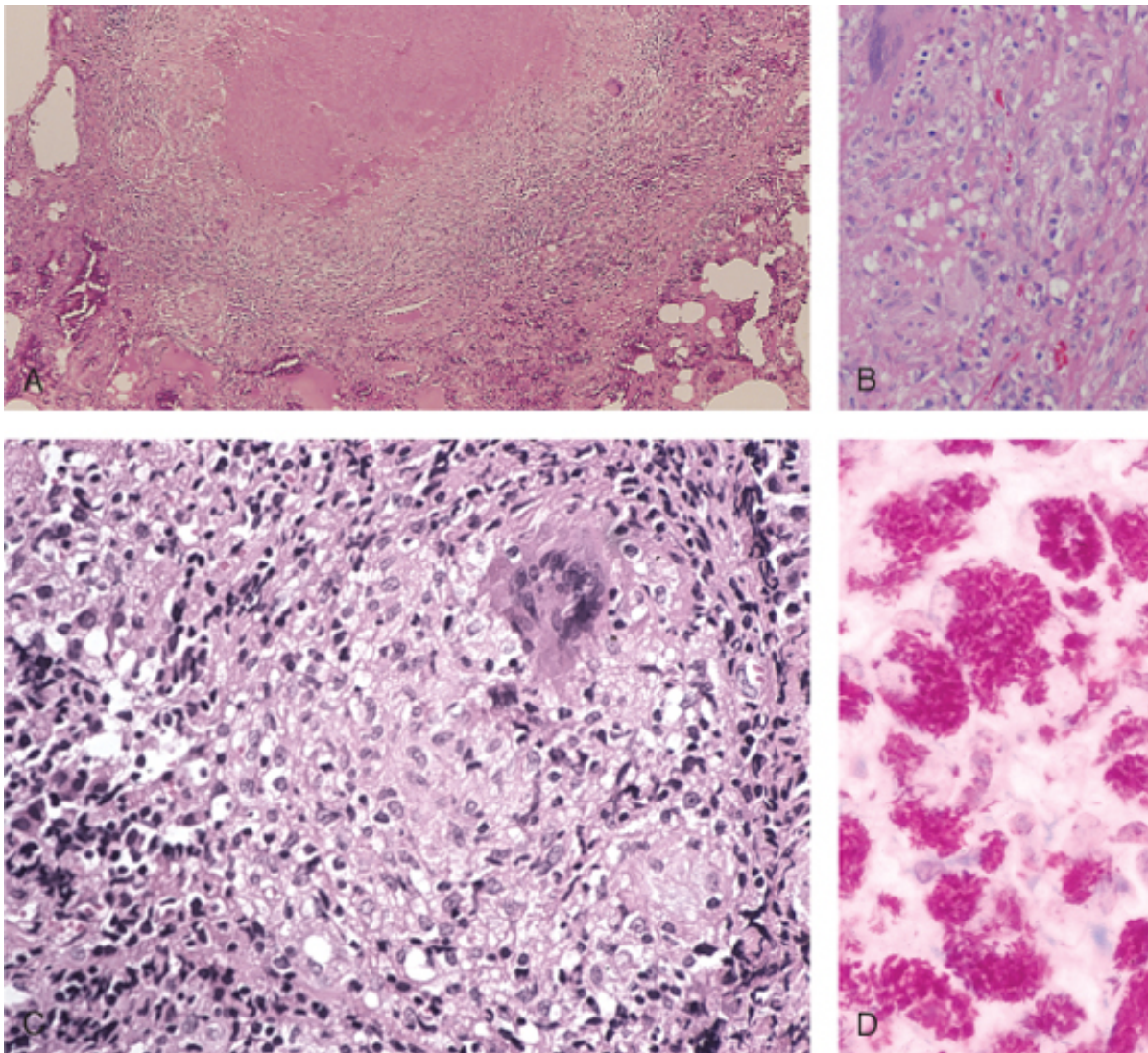
### Morphology

In countries where bovine tuberculosis and infected milk have largely disappeared, primary tuberculosis almost always begins in the lungs. Typically, the inhaled bacilli implant in the distal part of the upper lobe or the upper part of the lower lobe, usually close to the pleural surface. As the infection develops, a 1- to 1.5-cm area of gray-white inflammatory consolidation emerges, the center of which eventually undergoes caseous necrosis. Tubercle bacilli, either directly or indirectly, drain to the regional nodes, which also often caseate. **This combination of parenchymal involvement and lymph node caseation** is referred to as the Ghon complex (Fig. 13-35). During the first few weeks, the infection spreads by lymphatic and hematogenous dissemination to other parts of the body. In approximately 90% of cases, the development of cell-mediated immunity controls the infection. Hence, the Ghon complex usually undergoes progressive fibrosis, often followed by radiologically detectable calcification (Ranke's complex). In the absence of seeding of other organs, no lesions develop.

Histologically, sites of active involvement are marked by a characteristic granulomatous reaction that forms both caseating and noncaseating tubercles (Fig. 13-36A-C). In the early stage, the reaction is microscopic; it is only when multiple granulomas coalesce that they become macroscopic. Each granuloma is usually enclosed within a fibroblastic rim punctuated by lymphocytic cells. Giant cells are present in the granulomas.







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Figure 13-36 The morphologic spectrum of tuberculosis. **A** characteristic tubercle at low magnification (**A**) and in (**right**) that is surrounded by epithelioid and multinucleated giant cells (**left**). This is the usual response seen in immunity to the organism. **C**, Occasionally, even in immunocompetent individuals, tubercular granulomas may not show presence or absence of caseous necrosis, special stains for acid-fast organisms must be performed when granuloma. In immunosuppressed individuals, tuberculosis may not elicit a granulomatous response ("nonreactive tuberculosis" packed with mycobacteria that are demonstrable with acid-fast stains. (**D**, Courtesy of Dr. Dominick Cavuoti, D Southwestern Medical School, Dallas, Texas.)

The chief implications of primary tuberculosis are that (1) it induces hypersensitivity and increases the number of viable bacilli for years, perhaps for life, and thus be the nidus for *reactivation* at a later time and (3) uncommonly, the disease may develop without interruption into so-called *progressive primary tuberculosis* in individuals who are immunocompromised because of a defined illness such as AIDS or because of impaired host defenses, as may occur in malnourished children or in the elderly. Certain racial groups, such as the African Americans, are particularly susceptible to progressive primary tuberculosis. The incidence of progressive primary tuberculosis is particularly high in individuals with an advanced degree of immunosuppression (i.e., CD4<sup>+</sup> counts <200 cells/mm<sup>3</sup>). Immunosuppression interferes with the cell-mediated immunologic reaction that would contain the primary focus; because hypersensitivity is concomitant, the lack of a tissue hypersensitivity reaction results in the absence of the characteristic granulomatous response (Fig. 13-36D).



The diagnosis of progressive primary tuberculosis in adults can be difficult. Contrary to the usual primary tuberculosis (apical disease with cavitation, see below), progressive primary tuberculosis more often presents as pneumonia, with lower and middle lobe consolidation, hilar adenopathy, and pleural effusion; cavitation occurs only in the setting of severe immunosuppression. Lymphohematogenous dissemination is a dreaded complication and includes *tuberculous meningitis* and *miliary tuberculosis*. Because similar lesions also occur after progression of primary disease, they will be discussed later.

### Secondary Tuberculosis (Reactivation Tuberculosis)

*Secondary (or postprimary) tuberculosis is the pattern of disease that arises in a previously sensitized individual. It may result from reactivation of dormant primary lesions, most commonly when host resistance is weakened. It may also result from exogenous reinfection because of the primary disease or because of a large inoculum of virulent bacilli. Reactivation of endogenous disease is more common in prevalence areas, whereas reinfection plays an important role in regions of high contagion. Whereas only a few individuals (less than 5%) with primary disease subsequently develop secondary tuberculosis*

*Secondary pulmonary tuberculosis is classically localized to the apex of one or both upper lobes. This is due to the high oxygen tension in the apices. Because of the preexistence of hypersensitivity, the bacilli excite a reaction that tends to wall off the focus. As a result of this localization, the regional lymph nodes are less involved in the developing disease than they are in primary tuberculosis. On the other hand, cavitation occurs rarely in primary disease but is common in secondary disease, with dissemination along the airways. Indeed, cavitation is almost inevitable in neglected secondary tuberculosis. The person now becomes an important source of infectivity, because the person now raises sputum containing bacilli.*

Secondary tuberculosis should always be an important consideration in HIV-positive patients who are immunosuppressed. It is noteworthy that *while an increased risk of tuberculosis exists at all stages of HIV disease, the major risk is in the late stages of disease, with a high degree of immunosuppression*. For example, persons with less severe immunosuppression (CD4 counts  $>200$  cells/mm<sup>3</sup>) present with a clinical picture that resembles progressive primary tuberculosis (apical disease with cavitation, hilar lymphadenopathy, and noncavitary disease). The extent of immunosuppression is reflected by extrapulmonary involvement, rising from 10% to 15% in mildly immunosuppressed patients to greater than 50% in severe immune deficiency. *Other atypical features* in HIV-positive patients that make the diagnosis of tuberculosis difficult include an increased frequency of sputum-smear negativity for acid-fast bacilli compared with HIV-negative patients, the absence of cavitation and endobronchial damage is more in immunocompetent individuals and therefore in contrast, despite the higher tissue bacillary load, the absence of tissue (bronchial wall) destruction. Hypersensitivity results in fewer bacilli in the sputum. In addition, false-negative PPD because of tuberculin anergy and characteristic granulomas in tissues, particularly in the late stages of HIV infection, also render diagnosis difficult.

### Morphology

The initial lesion is usually a small focus of consolidation, less than 2 cm in diameter, located in the **apical pleura**. Such foci are sharply circumscribed, firm, gray-white to yellow areas of consolidation with a large amount of central caseation and peripheral fibrosis. In favorable cases, the initial process undergoes progressive fibrous encapsulation, leaving only fibrocalcific scars. Histologic studies show characteristic coalescent tubercles with central caseation. Although tubercles can be demonstrated by appropriate methods in early exudative and caseous phases of disease, it is usually impossible to find them in the late, fibrocalcific stages. Localized, apical, secondary tuberculosis may heal with fibrosis either spontaneously or after therapy, or the disease may extend along several different pathways:

**Progressive pulmonary tuberculosis** may ensue. The apical lesion enlarges with caseation. Erosion into a bronchus evacuates the caseous center, creating a ragged cavity lined by **caseous material** that is poorly walled off by fibrous tissue (Fig. 13-37). Erosion into a blood vessel leads to hemoptysis. With adequate treatment, the process may be arrested, although healing often distorts the pulmonary architecture. Irregular cavities, now free of caseation necrosis, are surrounded by fibrosis. If the treatment is inadequate, or if host defenses are overwhelmed, the disease spreads by direct expansion, via dissemination through airways, lymphatic channels, or hematogenous spread. **Miliary pulmonary disease** occurs when organisms drain through lymphatics into the venous system, empty into the venous return to the right side of the heart and thence into the pulmonary circulation. The lesions are either microscopic or small, visible (2 mm) foci of yellow-white consolidation.

lesions are either microscopic or small, visible (2-mm) foci of yellow-white consolidation in lung parenchyma (the word *miliary* is derived from the resemblance of these foci to millet seeds). Lesions may expand and coalesce to yield almost total consolidation of large regions of the lung. With progressive pulmonary tuberculosis, the pleural cavity is invariably involved. **Pleural effusions, tuberculous empyema, or obliterative fibrous pleuritis** may

**Endobronchial, endotracheal, and laryngeal tuberculosis** may develop when infection reaches the respiratory tract either through lymphatic channels or from expectorated infectious material. The mucosa is thickened and studded with minute granulomatous lesions, sometimes apparent only on microscopic examination.

**Systemic miliary tuberculosis** ensues when infective foci in the lungs seed the pleural space or the heart; the organisms subsequently disseminate through the systemic arterial system. Lesions in other parts of the body may be seeded. Lesions resemble those in the lung. Miliary tuberculosis involves the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epidural space.

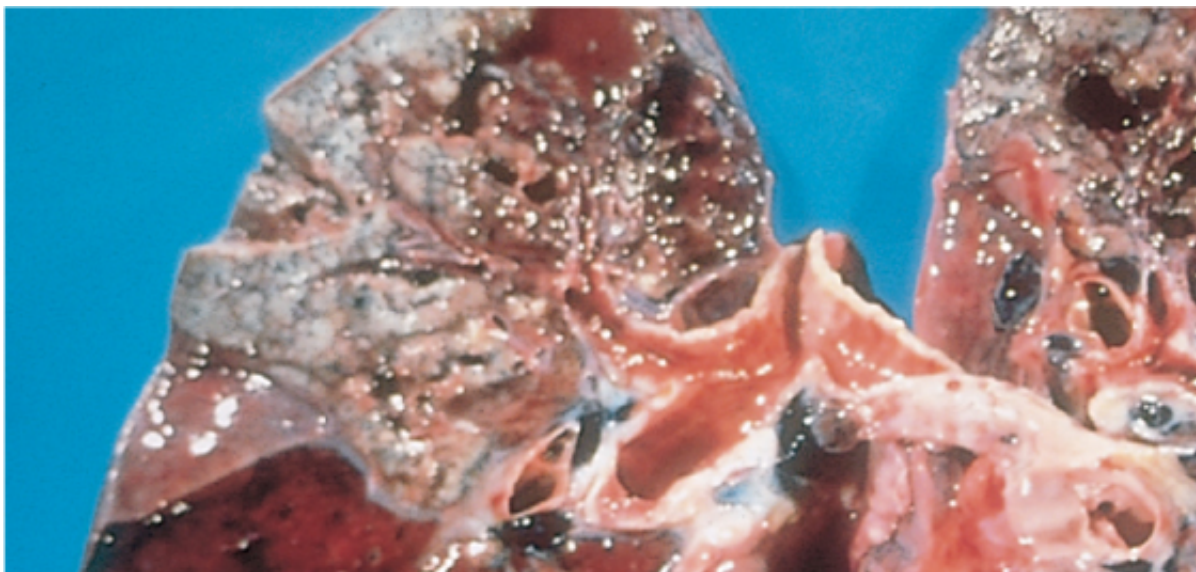
**Isolated-organ tuberculosis** may appear in any one of the organs or tissues seeded by the organisms. It may be the presenting manifestation of tuberculosis. Organs typically involved include the brain (tuberculous meningitis), kidneys (renal tuberculosis), adrenals (formerly an important cause of Addison disease), bones (osteomyelitis), and fallopian tubes (salpingitis). When the vertebral disease is referred to as Pott disease. Paraspinal "cold" abscesses in persons with tuberculosis may track along the tissue planes to present as an abdominal or pelvic mass.

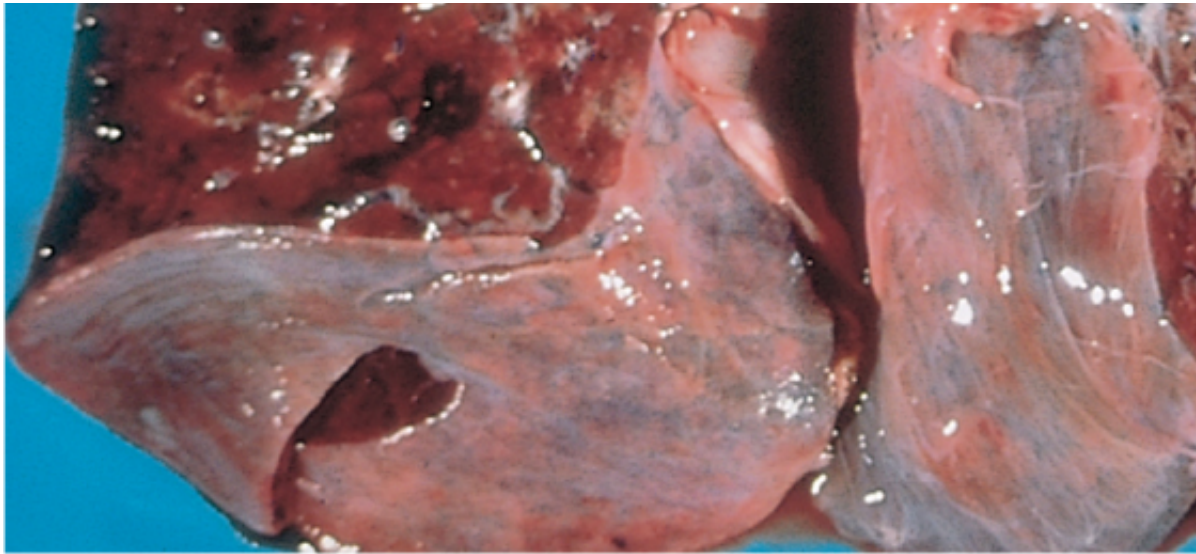
**Lymphadenitis** is the most frequent form of extrapulmonary tuberculosis, usually involving the cervical lymph node region ("scrofula"). In HIV-negative individuals, lymphadenopathy tends to be unifocal and localized. HIV-positive persons, on the other hand, often demonstrate multifocal disease, systemic symptoms, and either pulmonary or other forms of active tuberculosis.

In years past, **intestinal tuberculosis** contracted by the drinking of contaminated milk was a primary focus of tuberculosis. In developed countries today, intestinal tuberculosis is usually a complication of protracted advanced secondary tuberculosis, secondary to the swallowing of infectious material. Typically, the organisms are trapped in mucosal lymphoid aggregates in the ileocecal region of the large bowel, which then undergo inflammatory enlargement with ulceration of the mucosa, particularly in the ileum.

The many patterns of tuberculosis are depicted in [Figure 13-39](#).

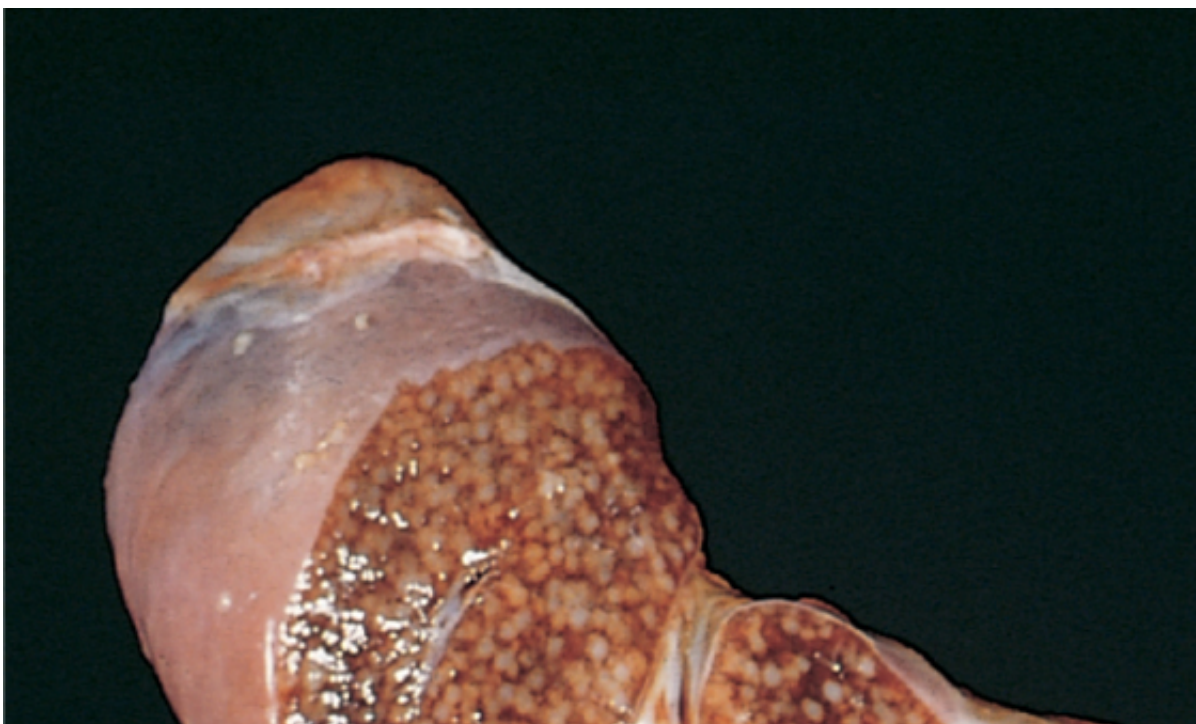
### Clinical Course



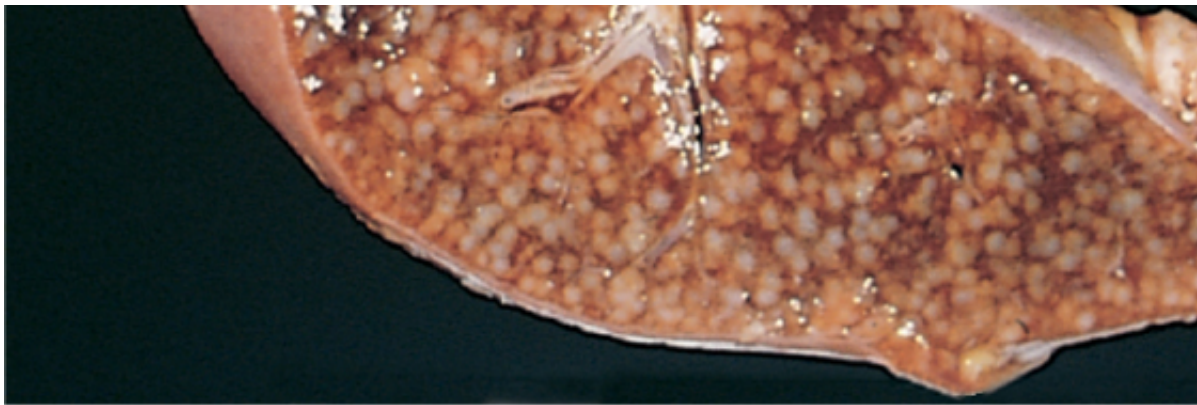


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 Figure 13-37 Secondary pulmonary tuberculosis. The upper parts of both lungs are riddled with gray-white areas of consolidation and cavitation.

Localized secondary tuberculosis may be asymptomatic. When manifestations appear, they are usually a combination of both systemic and localizing symptoms. Systemic symptoms, probably related to the release of cytokines by macrophages (e.g., TNF and IL-1), often appear early in the course and include malaise, anorexia, and *fever is low grade* and remittent (appearing late each afternoon and then subsiding), and *night sweats*. Localizing symptoms include increasing amounts of sputum, at first mucoid and later purulent, and the appearance of *hemoptysis*. Some degree of *hemoptysis* is present in about half of all cases of pulmonary tuberculosis. The diagnosis of pulmonary disease is based in part on the findings of *consolidation or cavitation in the apices of the lungs*. Ultimately, however, *tubercle bacilli* are the definitive finding.







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Figure 13-38 Miliary tuberculosis of the spleen. The cut surface shows numerous gray

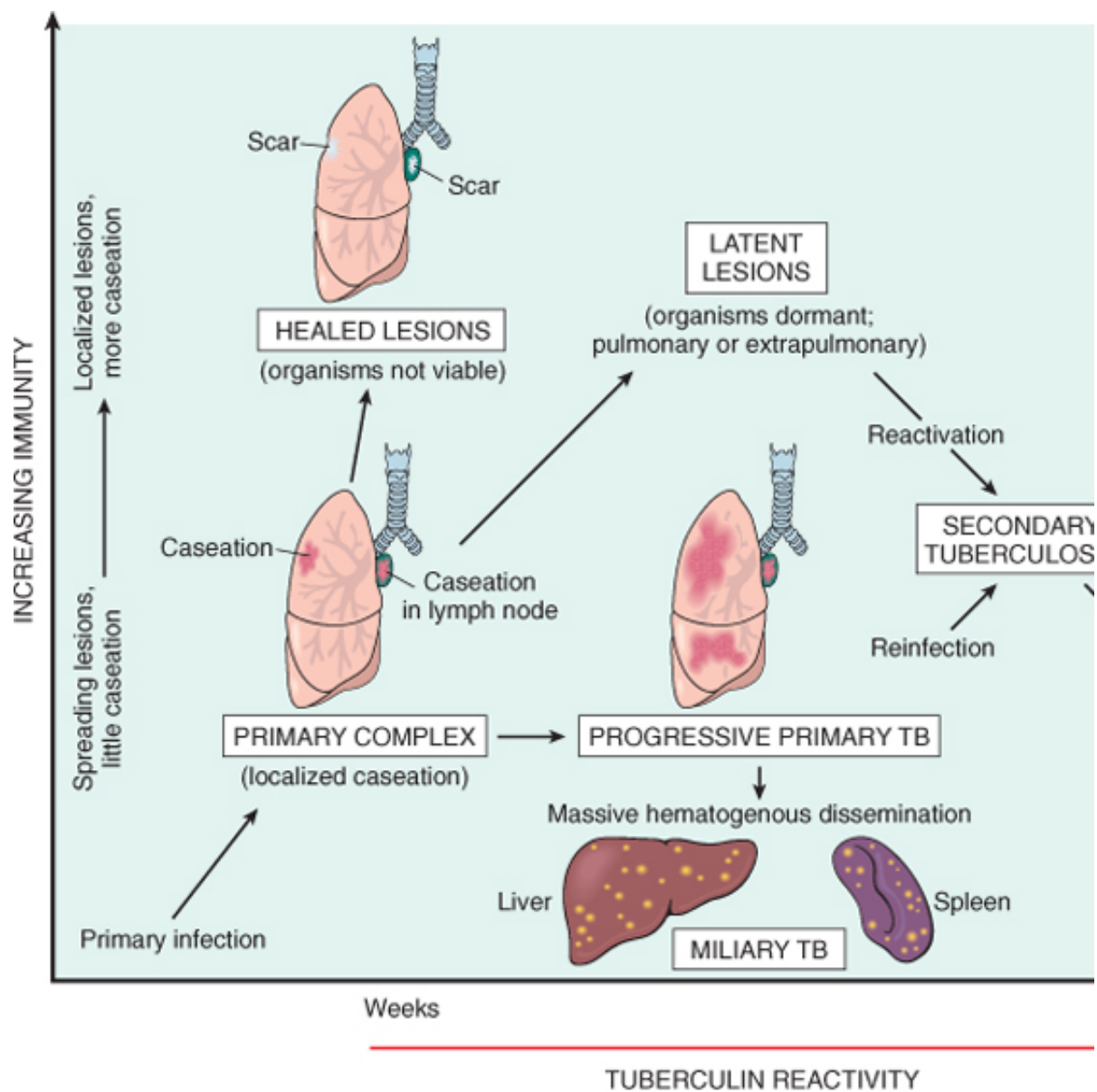




Figure 13-39 The natural history and spectrum of tuberculosis. (Adapted from a sketch provided by Dr. R. K. Kumar, Pathology, Sydney, Australia.)

The most common methodology for diagnosis of tuberculosis remains demonstration of acid-fast bacilli by use of fluorescent auramine rhodamine; most protocols require at least two sputum examinations for sputum negativity. Conventional cultures for mycobacteria require up to 10 weeks, but recent liquid culture systems that detect mycobacterial metabolism are able to provide an answer within 2 weeks. PCR amplification offers greater rapidity of diagnosis, and two such assays are currently approved for use in the United States. Sensitivity of 10 organisms in clinical specimens, compared with greater than 10,000 organisms required for smear microscopy, is the gold standard because it also allows testing of drug susceptibility. Multidrug resistance (MDR) tuberculosis, defined as two or more of the primary drugs used for treatment of tuberculosis, is now seen more commonly, and people worldwide may be infected with MDR-TB. This form of tuberculosis is of particular concern.

The prognosis of tuberculosis is generally favorable if infections are localized to the lungs, but it worsens if it occurs in the setting of aged, debilitated, or immunosuppressed persons, who are at high risk for complications. Those with MDR-TB. Amyloidosis may appear in persistent cases.

### SUMMARY

**Tuberculosis** It is a chronic granulomatous disease caused by *M. tuberculosis*. It primarily affects the lungs, but virtually any extra-pulmonary organ can be involved by isolated tuberculous infection. Exposure to mycobacteria results in development of an immune response that confers resistance to reinfection but also to hypersensitivity (as determined by a positive *tuberculin test*). CD4<sup>+</sup> T cells play a crucial role in the cell-mediated immunity against mycobacteria; mediators of cellular immunity for bacterial containment include IFN- $\gamma$ , IL-12, TNF, and nitric oxide synthase. The typical host reaction to tuberculosis in immunocompetent individuals is the formation of *granulomas*, usually with central caseating necrosis. Secondary (reactivation) tuberculosis occurs in previously exposed individuals when host immune defenses are compromised, leading to cavitary lesions in the lung apices. Both progressive primary tuberculosis and reactivation tuberculosis can result in systemic seeding, causing life-threatening forms such as miliary tuberculosis and tuberculous meningitis. HIV is a well known risk factor for development of tuberculosis.

### Nontuberculous Mycobacterial Disease

Nontuberculous mycobacteria most commonly cause chronic but clinically localized pulmonary disease. In the United States, strains implicated most frequently include *M. avium-intracellulare* (also called *M. abscessus*). It is not uncommon for nontuberculous mycobacteria to present as upper lobe cavitary lesions, especially in individuals with a long-standing history of smoking or alcoholism. The presence of chronic lung disease (COPD, cystic fibrosis, pneumoconiosis) is an important risk factor associated with nontuberculous mycobacterial disease.

In immunosuppressed individuals (primarily, HIV-positive patients), *M. avium* complex presents as a systemic infection with symptoms (fever, night sweats, weight loss). Hepatosplenomegaly and lymphadenopathy, due to involvement of the mononuclear phagocyte system by the opportunistic pathogen, is common, as are gastrointestinal malabsorption. Pulmonary involvement is often indistinguishable from tuberculosis in AIDS patients. Infection in AIDS patients tends to occur late in the course of the disease, when CD4 counts have fallen. Tissue examination usually does not reveal granulomas and, instead, foamy histiocytes "plugged" into alveolar spaces are seen.

### Histoplasmosis, Coccidioidomycosis, and Blastomycosis

The dimorphic fungi, which include *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*, cause pulmonary involvement as commonly seen in infected immunocompetent individuals, or in immunocompromised persons. T cell-mediated immune responses are critical for containing the infection.

compromised cell-mediated immunity, such as those with HIV, are more prone to systemic diseases. In clinical presentations, all three dimorphic fungi will be considered together in this section.

### Epidemiology

Each of the dimorphic fungi has a typical geographic distribution.

*H. capsulatum*: endemic in the Ohio and central Mississippi River valleys and along the Appalachian States. Warm, moist soil, enriched by droppings from bats and birds, provides the ideal medium for *H. capsulatum* and produces infectious spores.

*C. immitis*: endemic in the Southwest and Far West of the United States, particularly in California's Central Valley, as "valley fever."

*B. dermatitidis*: endemic area is confined in the United States to areas overlapping with those where *H. capsulatum* is endemic.

### Morphology

The yeast forms are fairly distinctive, which helps in the identification of individual fungi.

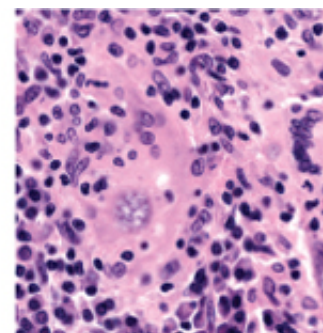
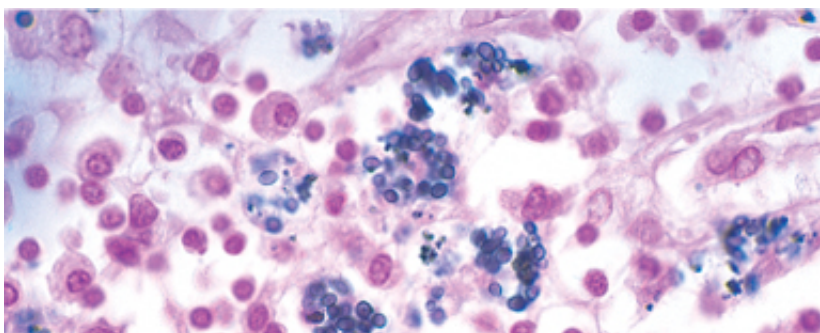
*H. capsulatum*: round to oval and small yeast forms measuring 2 to 5  $\mu\text{m}$  in diameter. *C. immitis*: thick-walled, nonbudding spherules, 20 to 60  $\mu\text{m}$  in diameter, often containing endospores (Fig. 13-40B). *B. dermatitidis*: round to oval and larger than *H. capsulatum* (2 to 5  $\mu\text{m}$  in diameter); reproduce by characteristic "broad-based" budding (Fig. 13-40C, D).

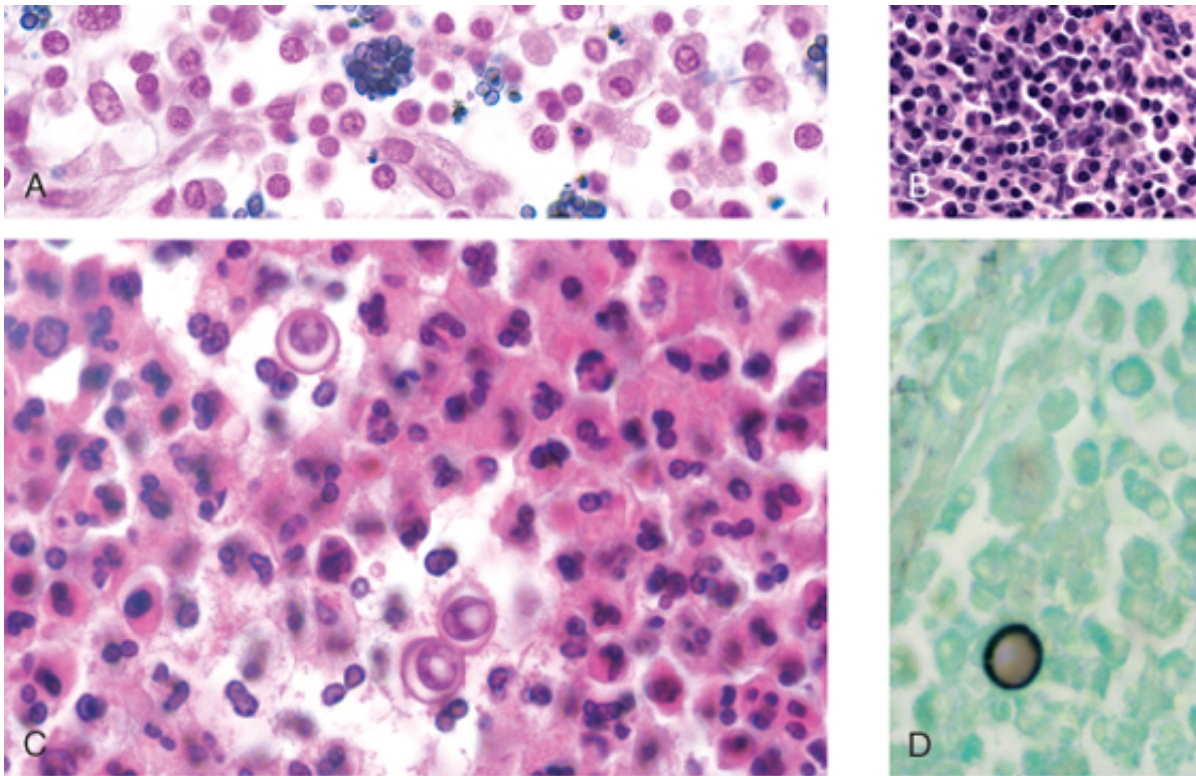
### Clinical Features

Clinical manifestations may take the form of (1) *acute (primary) pulmonary infection*, (2) *chronic (secondary) pulmonary infection*, or (3) *disseminated disease*. The primary pulmonary nodules, composed of aggregates of macrophages, are associated with similar lesions in the regional lymph nodes. These lesions develop into small granulomas that may develop central necrosis and later fibrosis and calcification. The similarity to primary tuberculosis requires identification of the yeast forms (best seen with periodic acid-Schiff or silver stains). The primary infection is usually self-limited. In the vulnerable host, chronic cavitary pulmonary disease develops, resembling the secondary form of tuberculosis. It is not uncommon for these fungi to give rise to bronchogenic carcinoma radiologically. At this stage, cough, hemoptysis, and even dyspnea and weight loss may occur.

In infants or immunocompromised adults, particularly those with HIV infection, disseminated disease may develop. Under these circumstances there are no well-formed granulomas. Instead, focal collections of organisms are seen within cells of the mononuclear phagocyte system, including in the liver, spleen, lymph nodes, and gastrointestinal tract, and bone marrow. The adrenals and meninges may also be involved, and in the nose and mouth, on the tongue, or in the larynx. Disseminated disease is a hectic, febrile illness with leukopenia, and thrombocytopenia. Cutaneous infections with disseminated *Blastomyces* organisms may produce hyperplasia, which may be mistaken for squamous cell carcinoma.

### Pneumonia in the Immunocompromised Host





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 Figure 13-40 **A**, *Histoplasma capsulatum* yeast forms fill phagocytes in a lymph node of a person with disseminated infection. **B**, High magnification of *H. capsulatum* yeast forms. **C**, Blastomycosis, with rounded budding yeasts, larger than most other fungi. **D**, Silver stain highlighting broad-based buds.

The appearance of a pulmonary infiltrate and signs of infection (e.g., fever) are some of the most common signs of infection in persons whose immune and defense systems are suppressed by disease, immunosuppression from chemotherapy, or irradiation. A wide variety of so-called opportunistic agents, many of which rarely cause infection in healthy persons, can cause pneumonias, and often more than one agent is involved. Examples of pulmonary opportunistic pathogens include (1) bacteria (*P. aeruginosa*, *Mycobacterium* spp., *L. pneumophila*, and *Listeria monocytogenes*); (2) viruses (cytomegalovirus, *P. jiroveci*, *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans*). Of these, we will discuss *P. jiroveci*, and the opportunistic fungal infections.

### Cytomegalovirus Infections

Cytomegalovirus (CMV), a member of the herpesvirus family, may produce a variety of disease manifestations in the infected host but even more so on the host's immune status. Cells infected by the virus exhibit characteristic changes. Within the nucleus is an enlarged inclusion surrounded by a clear halo ("owl's eye"), a characteristic feature of symptomatic disease that occurs in neonates, cytomegalic inclusion disease. Although classic CMV infections occur in many organs, CMV infections are discussed here because in immunosuppressed adults, particularly after allogeneic bone marrow transplants, CMV pneumonitis is a serious problem.

Transmission of CMV can occur by several mechanisms, depending on the age group affected:

A fetus can be infected transplacentally from a newly acquired or primary infection in the mother. The virus can also be transmitted to the fetus through cervical or vaginal secretions at birth, or, later, through breast milk. Preschool children, especially in day care centers, can acquire CMV infection readily and transmit the virus to their parents. In individuals over 15 years of age, the venereal route is the most common mode of transmission, but spread may also occur via respiratory secretions and the fecal-oral route. In immunosuppressed individuals, age through organ transplants or by blood transfusions.



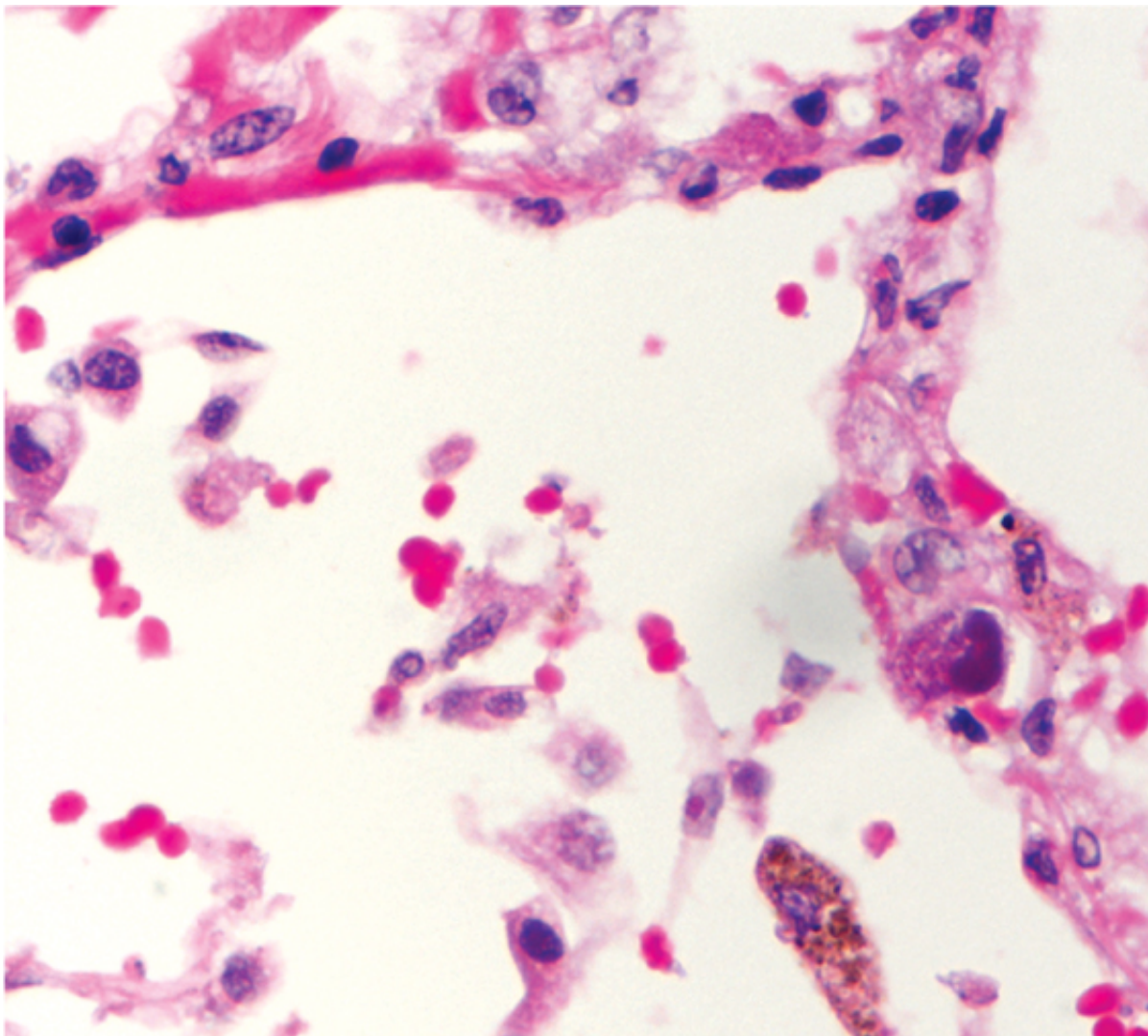
### **Morphology**

Histologically, the characteristic enlargement of cells can be appreciated. In the glomeruli, the glomerular epithelial cells are affected; in the brain, the neurons; in the lungs, the alveolar and endothelial cells; and in the kidneys, the tubular epithelial and glomerular cells. **Affected cells are strikingly enlarged, often to a diameter of 40  $\mu\text{m}$ , and they show nuclear polymorphism.** Prominent intranuclear basophilic inclusions spanning half the nucleus are usually set off from the nuclear membrane by a clear halo (Fig. 13-41). Within the cytoplasm, smaller basophilic inclusions may also be seen.

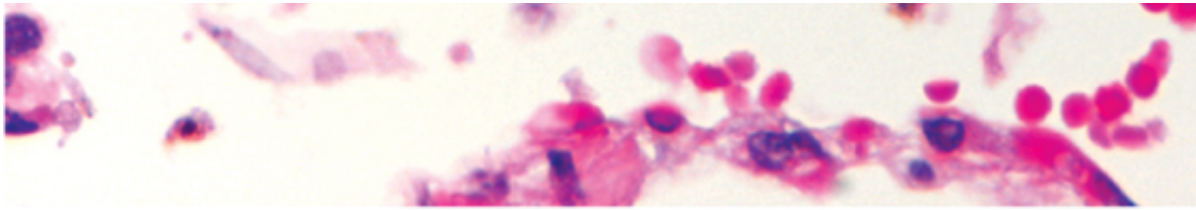
### *Cytomegalovirus Mononucleosis*

In healthy young children and adults, the disease is nearly always asymptomatic. In surveys around the world, 80-100% of adults demonstrate anti-CMV antibodies in the serum, indicating previous exposure. The most common clinical presentation in immunocompetent hosts beyond the neonatal period is an infectious mononucleosis-like illness, with lymphadenopathy, and hepatomegaly accompanied by abnormal liver function test results, suggesting recovery from CMV mononucleosis without any sequelae, although excretion of the virus may occur. Irrespective of the presence or absence of symptoms after infection, a person once infected becomes a lifelong carrier, remaining latent within leukocytes, which are the major reservoirs.

### *CMV in Immunosuppressed Individuals*







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 Figure 13-41 Cytomegalovirus infection of the lung. A typical distinct nuclear and ill-defined cytoplasmic inclusion in a cell (H&E stain, ×1000 magnification, from a patient at Brigham Young University and Women's Hospital, Boston, Massachusetts.)

This occurs most commonly in three groups:

*Recipients of organ transplants* (heart, liver, kidney) from seropositive donors. These individuals receive immunosuppressive therapy, and the CMV is usually derived from the donor organ, but reactivation of latent host may also occur. *Recipients of allogeneic bone marrow transplants*. These people are on immunosuppressive drug therapy but also because of graft-versus-host disease. In this setting there is usually reactivation of latent CMV. *Persons with AIDS*. These immunosuppressed individuals have reactivation of latent CMV. *CMV is the most common opportunistic viral pathogen in AIDS.*

In all these settings, serious, life-threatening disseminated CMV infections primarily affect the lung (pneumonitis), and retina (retinitis); the central nervous system is usually spared. In the pulmonary infection, areas of necrosis develop, accompanied by the typical enlarged cells with inclusions. The pneumonia is characterized by respiratory distress syndrome. Intestinal necrosis and ulceration can develop and be extensive, leading to "pseudomembranes" (Chapter 15) and debilitating diarrhea. CMV retinitis, by far the most common ocular infection, can occur either alone or in combination with involvement of the lungs and intestinal tract. Diagnosis is by demonstration of characteristic morphologic alterations in tissue sections, successful viral culture, qualitative or quantitative PCR-based detection of CMV DNA. The last approach has revolutionized diagnosis after transplantation.

### ***Pneumocystis Pneumonia***

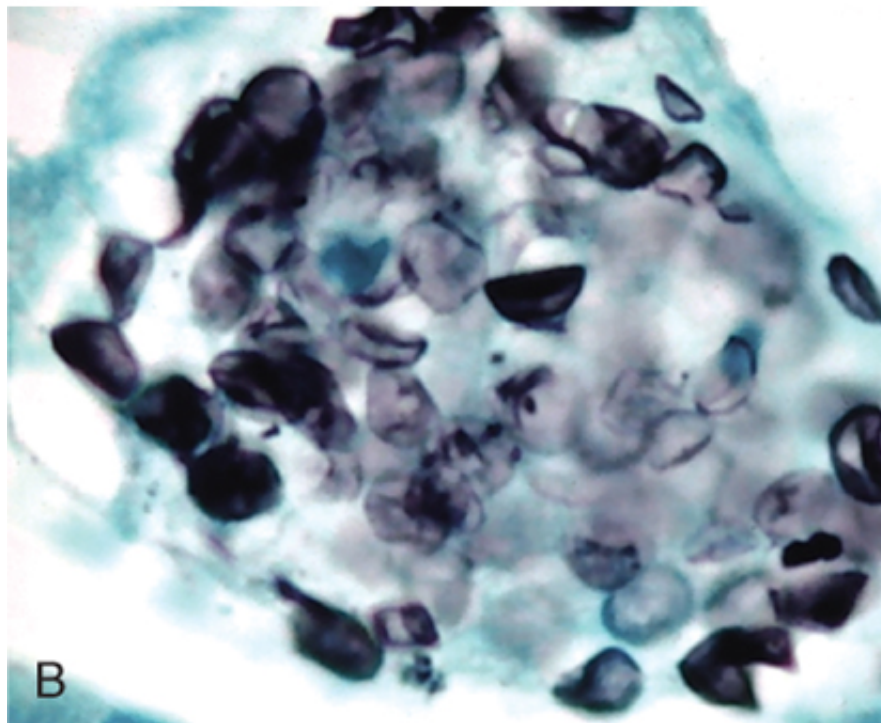
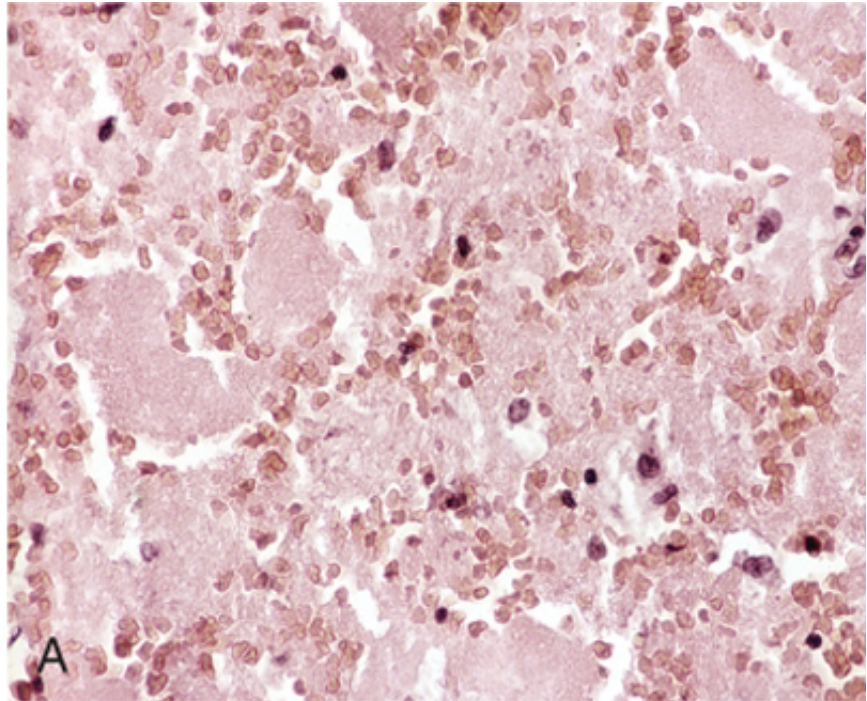
*P. jirovecii* (formerly known as *P. carinii*), an opportunistic infectious agent long considered to be a fungus, is closely related to fungi. Serologic evidence indicates that virtually all persons are exposed to *Pneumocystis*, but in most the infection remains latent. Reactivation and clinical disease occurs almost exclusively in immunosuppressed individuals (especially after organ transplantation or in individuals receiving corticosteroids). In AIDS patients, the risk of acquiring *P. jirovecii* infections increases in direct proportion to the degree of immunosuppression, with counts of less than 200 cells/mm<sup>3</sup> having a strong predictive value. *Pneumocystis* infections produce an interstitial pneumonitis.

### **Morphology**

Microscopically, involved areas of the lung demonstrate a characteristic **intra-alveolar exudate** with H&E stains ("cotton candy" exudate) (Fig. 13-42A), and the septa have a minimal mononuclear infiltrate. Special stains are required to visualize the organism in its trophozoite or encysted form. Silver stains of tissue sections reveal **cup-shaped cysts** (2–5 µm in diameter) in the alveolar exudates (Fig. 13-42B). If sputum production can be successfully induced, or **methylene blue** stains can demonstrate the trophozoite forms of the organism (with long filopodia) in about 50% of patients.

The diagnosis of *Pneumocystis* pneumonia should be considered in any immunocompromised individual with an abnormal chest radiograph. Fever, dry cough, and dyspnea occur in 90% to 95% of patients, who also have peripheral and basilar infiltrates. Hypoxia is frequent; pulmonary function studies show a restrictive lung defect. The method of diagnosis is to identify the organism in bronchoalveolar lavage fluids or in a transbronchial biopsy.

histologic stains mentioned already, immunofluorescence antibody kits and PCR-based assays have been used to detect *Pneumocystis* in clinical specimens. If treatment is initiated before widespread involvement, the outlook for recovery is good. If treatment is initiated late, organisms are likely to remain, particularly in AIDS patients, relapses are common unless the underlying immunodeficiency and suppressive therapy is given.



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Figure 13-42 *Pneumocystis* pneumonia. A, The alveoli are filled with a characteristic foamy "cotton candy" exudate. B, High-power view of the exudate showing numerous small, dark, crescent-shaped structures (Pneumocystis carinii) within the exudate.

## Opportunistic Fungal Infection

### Candidiasis

*Candida albicans* is the most frequent disease-causing fungus. It is a normal inhabitant of the oral cavity in many individuals. Even though systemic candidiasis (with associated pneumonia) is a disease of immunocompromised patients, we will consider the protean manifestations of *Candida* species in this section.

#### Morphology

In tissue sections, *C. albicans* demonstrates yeastlike forms (blastoconidia), pseudohyphae (Fig. 13-43A). Pseudohyphae are an important diagnostic clue for *C. albicans* and consist of cells joined end to end at constrictions, thus simulating true fungal hyphae. The organism is stained with routine hematoxylin and eosin stains, but a variety of special "fungal" stains (Gomori's methenamine silver, periodic acid-Schiff) are commonly used to better highlight the pathogens.

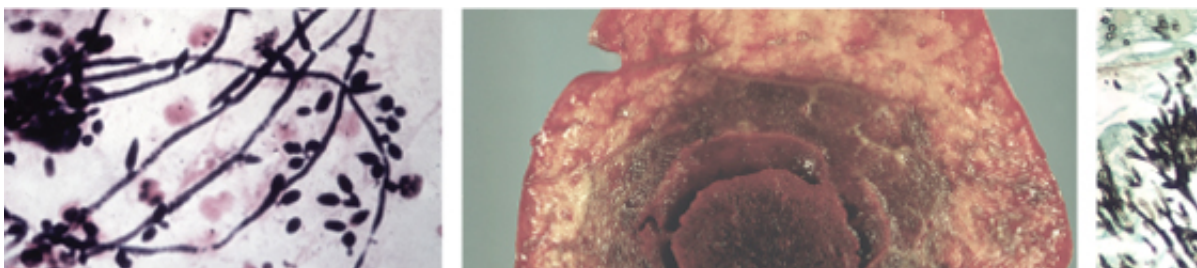
#### Clinical Syndromes

Candidiasis can involve the mucous membranes, skin, and deep organs (invasive candidiasis).

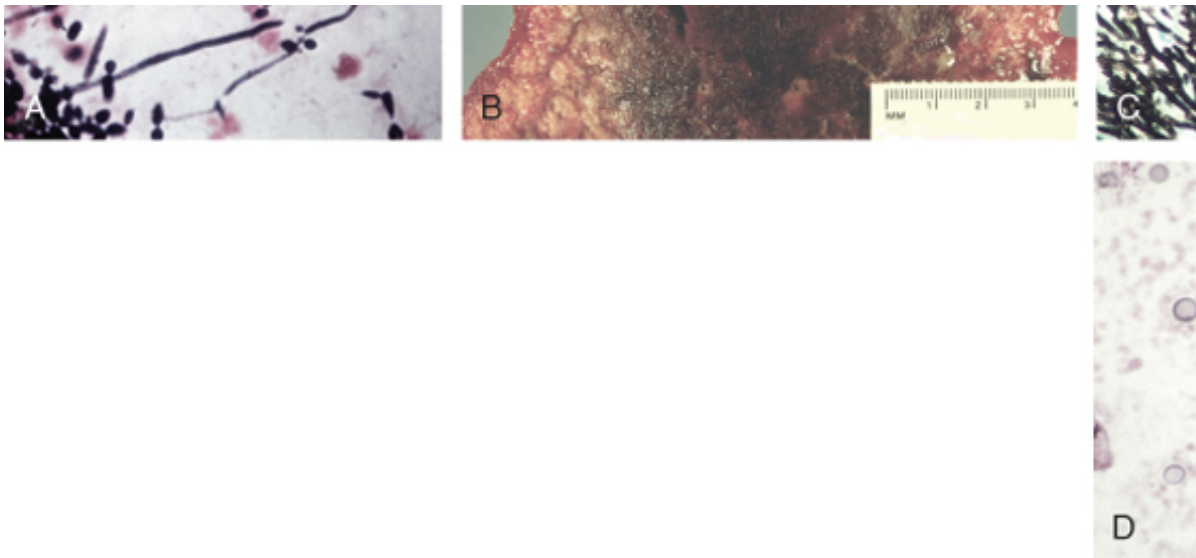
*The most common pattern of candidiasis takes the form of a superficial infection on mucous membranes. Florid proliferation of the fungi creates gray-white, dirty-looking pseudomembranes composed of inflammatory debris. Deep to the surface, there is mucosal hyperemia and inflammation. This is seen in newborns, debilitated patients, children receiving oral corticosteroids for asthma, and after antibiotic therapy that destroy competing normal bacterial flora. The other major risk group includes HIV-positive patients, for whom no obvious reason should be evaluated for HIV infection. Candida vaginitis is an extremely common infection in women, especially those who are diabetic or pregnant or on oral contraceptive pills. It is usually associated with a thick, curdlike discharge. Candida esophagitis is common in AIDS patients and in those with immunosuppression. Patients present with dysphagia (painful swallowing) and retrosternal pain; endoscopy demonstrates pseudomembranes resembling oral thrush on the esophageal mucosa. Cutaneous candidiasis includes infection of the nail proper ("onychomycosis"), nail folds ("paronychia"), hair follicles (such as armpits or webs of the fingers and toes ("intertrigo"), and penile skin ("balanitis"). Candida is also a candidal infection seen in the perineum of infants, in the region of contact of wet diapers. Chronic refractory disease afflicting the mucous membranes, skin, hair, and nails; it is associated with immunodeficiency. Associated conditions include endocrinopathies (most commonly hypoparathyroidism and diabetes mellitus) and autoantibodies. Disseminated candidiasis is rare in this disease. Invasive candidiasis implies invasion of the organism into various tissues or organs. Common patterns include (1) renal abscesses, (2) myocardial involvement (most commonly meningitis, but parenchymal microabscesses occur), (3) endocarditis, (4) splenic involvement, (5) hepatic abscesses, and (6) Candida pneumonia, usually presenting as a pneumonia (see above). Patients with acute leukemias who are profoundly immunosuppressed are particularly prone to developing systemic disease. Candida endocarditis is the most common form of endocarditis in patients with prosthetic heart valves or in intravenous drug abusers.*

### Cryptococcosis

*Cryptococcosis*, caused by *C. neoformans*, rarely occurs in healthy persons. It almost exclusively affects immunocompromised hosts, particularly those with AIDS or hematolymphoid malignancies.







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Figure 13-43 The morphology of fungal infections. **A**, The diagnosis of candidiasis is made by observing the ch (budding yeasts) in tissue sections or exudates. **B**, Invasive aspergillosis of the lung in a bone marrow transplan stained with Gomori methenamine-silver (GMS) stain, show septate hyphae with acute-angle branching, featur *Aspergillus* may demonstrate so-called fruiting bodies (*inset*) when it grows in areas that are well-aerated (such as the lung in a patient with AIDS). The yeast forms are somewhat variable in size; unlike in *Candida*, pseudohyphae a Cavuoti, Department of Pathology, University of Texas Southwestern Medical Schoo

### Morphology

The fungus, a 5- to 10- $\mu$ m yeast, has a thick, gelatinous capsule and reproduces b Unlike in *Candida*, however, pseudohyphal or true hyphal forms are not seen. **The diagnosis:** (1) In routine H & E stains, the capsule is not directly visible but often a surrounding the individual fungi representing the area occupied by the capsule. It is periodic acid-Schiff stains and effectively highlights the fungus; and (2) the capsule is the substrate for the cryptococcal latex agglutination assay, which is positive in c patients infected with the organism.

### Clinical Syndromes

Human cryptococcosis usually manifests as *pulmonary, central nervous system, or disseminated* acquired by inhalation from the soil or from bird droppings. *The fungus initially localizes in the lung particularly the meninges.* Sites of involvement are marked by a variable tissue response, which r gelatinous organisms with a minimal or absent inflammatory cell infiltrate (in immunodeficient hos more reactive host). In immunosuppressed patients, fungi grow in gelatinous masses within the m Virchow-Robin spaces, producing the so-called soap-bubble lesions.

### The Opportunistic Molds

*Mucormycosis* and *invasive aspergillosis* are uncommon infections almost always limited to immu with hematolymphoid malignancies, profound neutropenia, corticosteroid therapy, or post allogene

### Morphology

Mucormycosis is caused by the class of fungi known as Zygomycetes. Their hyphae branch at right angles; in contrast, the hyphae of *Aspergillus* species are **septate** a angles (Fig. 13-43C). *Rhizopus* and *Mucor* are the two fungi of medical importance class. Both Zygomycetes and *Aspergillus* cause a nondistinctive, suppurative, som reaction with a **predilection for invading blood vessel walls, causing vascular**



## Clinical Syndromes

**Rhinocerebral and pulmonary mucormycosis:** Zygomycetes have a propensity to colonize the nasal cavity and extend directly into the brain, orbit, and other head and neck structures. Patients with diabetes mellitus are at high risk for the fulminant invasive form of rhinocerebral mucormycosis. Pulmonary disease can be localized (e.g., cavitary lesions) or disseminated (e.g., radiologically with diffuse "miliary" involvement).

**Invasive aspergillosis** occurs almost exclusively in patients who are immunosuppressed. The fungus most often presents as a necrotizing pneumonia (see Fig. 13-43B). As mentioned previously, the fungus can invade blood vessels, and thus systemic dissemination, especially to the brain, is often a fatal complication.

**Allergic bronchopulmonary aspergillosis** occurs in patients with asthma who develop an exaggerated hypersensitivity against the fungus growing in the bronchi. These patients often have circulating IgE antibodies and peripheral eosinophilia.

**Aspergilloma** ("fungus ball") occurs by colonization of preexisting pulmonary cavities (e.g., cavitary lesions) by the fungus; these may act as ball valves, occluding the cavity and thus predisposing to hemorrhage.

## Pulmonary Disease in HIV Infection

Pulmonary disease continues to be the leading cause of morbidity and mortality in HIV-infected patients. Although the widespread use of antiretroviral agents and effective chemoprophylaxis has markedly altered the incidence and outcome of many pulmonary diseases, the plethora of entities involved makes diagnosis and treatment a distinct challenge. Some of the most common and potentially life-threatening pulmonary diseases afflicting HIV-infected persons have already been discussed; this section will focus only on the general principles of diagnosis and management of pulmonary disease.

Despite the emphasis on "opportunistic" infections, it must be remembered that bacterial pneumonia remains one of the most serious pulmonary disorders in HIV infection. The most common bacterial pathogens are *S. pneumoniae*, *S. aureus*, *H. influenzae*, and gram-negative rods. Bacterial pneumonias in HIV-infected individuals are more severe, and more often associated with bacteremia than in those without HIV infection. A host of noninfectious diseases, including Kaposi's sarcoma, lymphoma, and primary lung cancer, occur with increased frequency in HIV-infected individuals and must be excluded. The CD4+ T cell count is often useful in narrowing the differential diagnosis. As a general rule, opportunistic infections are more likely at lower CD4 counts (<200 cells/mm<sup>3</sup>); *Pneumocystis pneumonia* is more common at CD4 counts <200 cells/mm<sup>3</sup>, while CMV and *M. avium* complex infections are uncommon until the very late stages of HIV infection (CD4 counts <50 cells/mm<sup>3</sup>).

Finally, it is useful to remember that pulmonary disease in HIV-infected individuals may result from common pathogens that may present with atypical manifestations. Therefore, the diagnostic work-up for pulmonary disease in HIV-infected patients should be more extensive than would be mandated in an immunocompetent individual.





## LUNG TUMORS

Although lungs are frequently the site of metastases from cancers in extrathoracic organs, primary Bronchial epithelium is the site of origin of 95% of primary lung tumors (carcinomas); the remainder includes bronchial carcinoids, mesenchymal malignancies (e.g., fibrosarcomas, leiomyomas), lymphoma. The most common benign lesions are spherical, small (3-4 cm), discrete hamartomas that often show radiographically. They consist mainly of mature cartilage but are often admixed with fat, fibrous tissue in various proportions.

### Carcinomas

Carcinoma of the lung (also known as "lung cancer") is without doubt the number one cause of cancer deaths in many countries. It has long held this position among males in the United States, accounting for about 30% of all cancer deaths, and has become the leading cause of cancer deaths in women as well. The American Cancer Society estimates that in 2014, 158,000 individuals were diagnosed with lung cancer and 163,510 will die from it. The rate of increase among males has slowed, but continues to accelerate among females, with more women dying each year from lung cancer than from breast cancer. These statistics are undoubtedly related to the causal relationship of cigarette smoking and lung cancer. Lung cancer occurs in persons in their 50s and 60s. At diagnosis, more than 50% of individuals already have distant metastases and have disease in the regional lymph nodes. The prognosis of lung cancer is dismal: the 5-year survival rate for all stages combined is about 15%; even those with disease localized to the lung have a 5-year survival of approximately 50%.

The four major histologic types of carcinomas of the lung are squamous cell carcinoma, adenocarcinoma, small cell carcinoma (Table 13-8). In some cases there is a combination of histologic patterns (e.g., combined squamous and adenocarcinoma). For reasons not entirely understood, but probably due to changes in smoking habits, adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung tumor in recent years. Adenocarcinoma is the most common primary tumor arising in women, in lifetime nonsmokers, and in persons younger than 40 years. In addition to the types are discussed, some general principles underlying classification of lung tumors are presented.

For therapeutic purposes, carcinomas of the lung are classified into two broad groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The latter category includes squamous cell, adenocarcinoma, and large cell carcinoma. *for this distinction is that virtually all SCLCs have metastasized by the time of diagnosis and are best treated by chemotherapy, with or without radiation.* In contrast, NSCLCs are better treated by surgery. In addition to the differences in morphology and response to treatment (Table 13-9), there are also pertinent genetic differences between SCLC and NSCLC. Although the G<sub>1</sub>-S cell cycle checkpoint is abrogated in most lung carcinomas, it occurs via different mechanisms. NSCLCs are characterized by a high frequency of *RB* gene mutations, while the *p16/CDKN2A* gene is mutated in most SCLCs. Similarly, activating *KRAS* and *EGFR* oncogene mutations are virtually restricted to adenocarcinoma and are rare in SCLCs.

**Table 13-8. Histologic Classification of Malignant Epithelial Lung Tumors**

Squamous cell carcinoma
Adenocarcinoma
Acinar, papillary, solid, bronchioloalveolar, mixed subtypes
Large-cell carcinoma
Large-cell neuroendocrine carcinoma
Small-cell carcinoma
Combined small-cell carcinoma
Adenosquamous carcinoma

Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Spindle cell carcinoma
Giant-cell carcinoma
Carcinoid tumor
Typical, atypical
Carcinomas of salivary gland type
Unclassified carcinoma

Squamous cell, adenocarcinoma, large cell carcinoma are collectively referred to as non-small-cell lung carcinoma (NSCLC).

### *Etiology and Pathogenesis*

Carcinomas of the lung, similar to cancers at many other anatomic sites, arise by a stepwise accumulation of mutations that result in transformation of benign bronchial epithelium into neoplastic tissue. The sequence of mutations is not a predictable sequence that parallels the histologic progression toward cancer. Thus, inactivation of the *Rb* gene located on chromosome 13p is a very early event, whereas *p53* mutations or activation of the *KRAS* gene, located on chromosome 12p, is a later event. Importantly, it seems that certain genetic changes such as loss of chromosome 3p material, can be found in the bronchial epithelium of individuals with lung cancer, as well as in the respiratory epithelium of smokers without cancer. These areas of the respiratory mucosa are mutagenized after exposure to carcinogens ("field effect"). Over time, these areas accumulate additional mutations ultimately develop into cancer. A subset of adenocarcinomas, particularly those found in women of Far Eastern origin, harbor activating mutations of the *epidermal growth factor receptor* (*EGFR*). These tumors are profoundly susceptible to a class of agents that inhibit EGFR signaling, probably because the *EGFR* is "addicted" to the presence of a constitutively activated oncogene. The identification of a defined genetic target for therapy represents one of the successes in the rapidly expanding field of molecular medicine.

With regard to carcinogenic influences, there is strong evidence that *cigarette smoking* and, to a lesser extent, *radon exposure* are the main culprits responsible for the genetic changes that give rise to lung cancers. First, the history of smoking will be given, followed by a few brief comments on the less important influences.

*An impressive body of statistical, clinical, and experimental evidence incriminates cigarette smoking as the primary cause of lung cancer.* Statistically, about 90% of lung cancers occur in active smokers or those who stopped recently. The risk of developing lung cancer increases with the frequency of lung cancer and pack-years of cigarette smoking. The increased risk becomes 60 times greater in smokers (two packs a day for 20 years) compared with nonsmokers. For reasons not entirely clear, the risk of developing lung cancer is higher in smokers than men. Although cessation of smoking decreases the risk of developing lung cancer, it does not return to baseline levels. In fact, genetic changes that predate lung cancer can persist for many years in former smokers. Passive smoking (proximity to cigarette smokers) increases the risk of developing lung cancer in nonsmokers. The smoking of pipes and cigars also increases the risk, but only modestly.

**Table 13-9. Comparison of Small-Cell Lung Carcinoma (SCLC) and Non-Small Cell Lung Carcinoma (NSCLC)**

	SCLC	NSCLC
<b>Histology</b>		
	Scant cytoplasm; small, hyperchromatic nuclei with fine chromatin pattern; nucleoli indistinct; diffuse sheets of cells	Abundant cytoplasm; large, pleomorphic nuclei with coarse chromatin; prominent nucleoli
<b>Neuroendocrine Markers</b>		
For example, dense core granules on electron microscopy; expression of chromogranin, neuron-specific enolase and synaptophysin	Usually present	Usually absent
<b>Epithelial Markers</b>		
Epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin intermediate filaments	Present	Present
<b>Mucin</b>		
	Absent	Present in many types
<b>Peptide Hormone Production</b>		

<b>Peptide Hormone Production</b>		
	Adrenocorticotrophic hormone, antidiuretic hormone, gastrin-releasing peptide, calcitonin	Parathyroid hormone, calcitonin
<b>Tumor Suppressor Gene Abnormalities</b>		
3p deletions	>90%	>80%
RB mutations	~90%	~20%
p16/CDKN2A mutations	~10%	>50%
p53 mutations	>90%	>50%
<b>Dominant Oncogene Abnormalities</b>		
KRAS mutations	Rare	~30% (adenocarcinoma)
EGFR mutations	Absent	~20% (adenocarcinoma)
<b>Response to Chemotherapy and Radiotherapy</b>		
	Often complete response but recur invariably	Uncommon

Adapted and modified with permission from Minna JD: Neoplasms of the lung. In Fauci A, et al. (eds): In Harrison's Principles of Internal Medicine, 1998.

The *clinical evidence* is largely composed of the documentation of progressive morphologic alterations in the respiratory tract in habitual cigarette smokers. These sequential changes have been best documented in the bronchus, but they may also be present in other histologic subtypes. In essence, there is a linear correlation between cigarette smoke and the appearance of ever more worrisome epithelial changes that begin with reactive squamous metaplasia and progress to squamous dysplasia and carcinoma in situ, before culminating in invasive carcinoma. *histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with cigarette smoking.*

The *experimental evidence*, although it mounts with each passing year, lacks one important link: it has not been possible to induce lung cancer in an experimental animal by exposing it to cigarette smoke. Nonetheless, cigarette smoke contains numerous tumorigenic delicacies such as polycyclic hydrocarbons and other potent mutagens and carcinogens. In the experimental model, the chain of evidence linking cigarette smoking to lung cancer grows ever stronger.

Other influences may act in concert with smoking or may by themselves be responsible for some of the incidence of this form of neoplasia in miners of radioactive ores; asbestos workers; and workers exposed to chromium, uranium, nickel, vinyl chloride, and mustard gas. Exposure to asbestos increases the risk of lung cancer. By contrast, *heavy smokers exposed to asbestos have an approximately 55 times greater risk of developing lung cancer than those exposed to asbestos alone.*

Even though smoking and other environmental influences are paramount in the causation of lung cancer, not all individuals exposed to tobacco smoke do not develop cancer. It is very likely that the mutagenic effect of carcinogens is modified by (genetic) factors. Recall that many chemicals (procarcinogens) require metabolic activation via the cytochrome P-450 system for conversion into ultimate carcinogens (Chapter 6). There is evidence that persons with specific polymorphisms of the CYP2D6 gene have an increased capacity to metabolize procarcinogens derived from cigarette smoke. Similarly, individuals whose peripheral blood lymphocytes undergo chromosomal changes when exposed to tobacco-related carcinogens (mutagen sensitivity genotype) have a greater than 10-fold risk of developing lung cancer than controls.

### Morphology

Carcinomas of the lung begin as small mucosal lesions that are usually firm and grow as intraluminal masses, invade the bronchial mucosa, or form large bulky masses pushing into the lung parenchyma. Some large masses undergo cavitation caused by central necrosis or hemorrhage. Finally, these tumors may extend to the pleura, invade the pleural cavity, and spread to adjacent intrathoracic structures. More distant spread can occur via the hematogenous route.

**Squamous cell carcinomas** are more common in men than in women and are closely associated with a long smoking history; they tend to **arise centrally in major bronchi** and eventually spread to the periphery.



but they disseminate outside the thorax later than other histologic types. Large lesion necrosis, giving rise to **cavitation**. The preneoplastic lesions that antedate, and us squamous cell carcinoma are well characterized. Squamous cell carcinomas are o **squamous metaplasia or dysplasia** in the bronchial epithelium, which then trans **situ**, a phase that may last for several years (Fig. 13-44). By this time, atypical cell cytologic smears of sputum or in bronchial lavage fluids or brushings, although the and undetectable on radiographs. Eventually, the small neoplasm reaches a sympt well-defined tumor mass begins to obstruct the lumen of a major bronchus, often p and infection. Simultaneously, the lesion invades surrounding pulmonary substanc Histologically, these tumors range from well-differentiated squamous cell neoplas and intercellular bridges to poorly differentiated neoplasms having only minimal res features.

**Adenocarcinomas** may occur as central lesions like the squamous cell variant but **peripherally located**, many arising in relation to peripheral lung scars ("scar carcin basis for this association is not clear, although the current thinking is that the scarri secondary to the tumor, rather than being contributory. Adenocarcinomas are the r cancer in women and nonsmokers. In general, adenocarcinomas grow slowly and do the other subtypes, but they tend to metastasize widely at an early stage. Histol variety of forms, including **acinar (gland forming)** (Fig. 13-46C), **papillary**, and **sc** variant often requires demonstration of intracellular mucin production by special st adenocarcinomatous lineage. Although foci of squamous metaplasia and dysplasia epithelium proximal to resected adenocarcinomas, these are not the precursor lesi putative precursor of peripheral adenocarcinomas has been described as **atypical hyperplasia** (AAH) (Fig. 13-46A). Microscopically, AAH is recognized as a well-de epithelial proliferation composed of cuboidal to low-columnar cells resembling Clara pneumocytes, which demonstrate various degrees of cytologic atypia (nuclear hyp pleomorphism, prominent nucleoli), but not to the extent seen in frank adenocarcin have shown that lesions of AAH are monoclonal, and they share many of the mole associated with adenocarcinomas (e.g., *KRAS* mutations).

**Bronchioloalveolar carcinomas** (BACs) are included as a subtype of adenocarci classification of lung tumors. They involve peripheral parts of the lung, either as a s often, as multiple diffuse nodules that may coalesce to produce pneumonia-like col **feature of BACs is their growth along preexisting structures and preservation** (see Fig. 13-46B). The tumor cells grow in a monolayer on top of the alveolar septa scaffold (this has been termed a "lepidic" growth pattern, an allusion to the neoplas butterflies sitting on a fence). By definition, BACs do not demonstrate destruction o stromal invasion with desmoplasia, features that would merit their classification as The two subtypes of BACs are mucinous and nonmucinous, with the former compr with prominent cytoplasmic and intra-alveolar mucin. Analogous to the adenoma-c colon, it is proposed that some invasive adenocarcinomas of the lung may arise th **adenomatous hyperplasia-bronchioloalveolar carcinoma-invasive adenocarc** important to stress, however, that not all adenocarcinomas arise in this manner, no invasive if left untreated. While the cell types giving rise to the centrally located squ (metaplastic squamous cells in the main stem bronchi) and small cell lung carcinor cells, *see below*) were recognized for a while, the "cell of origin" for peripheral adei unclear until recently. Studies of lung injury models in mice have now identified a p cells at the bronchioalveolar duct junction, termed **bronchioalveolar stem cells** (E peripheral lung injury, the multipotent BASCs undergo expansion, replenishing the (bronchiolar Clara cells and alveolar cells) found in this location, thereby facilitat is postulated that BASCs incur the initiating oncogenic event (for example, a soma enable these cells to escape normal "checkpoint" mechanisms and result in pulmo

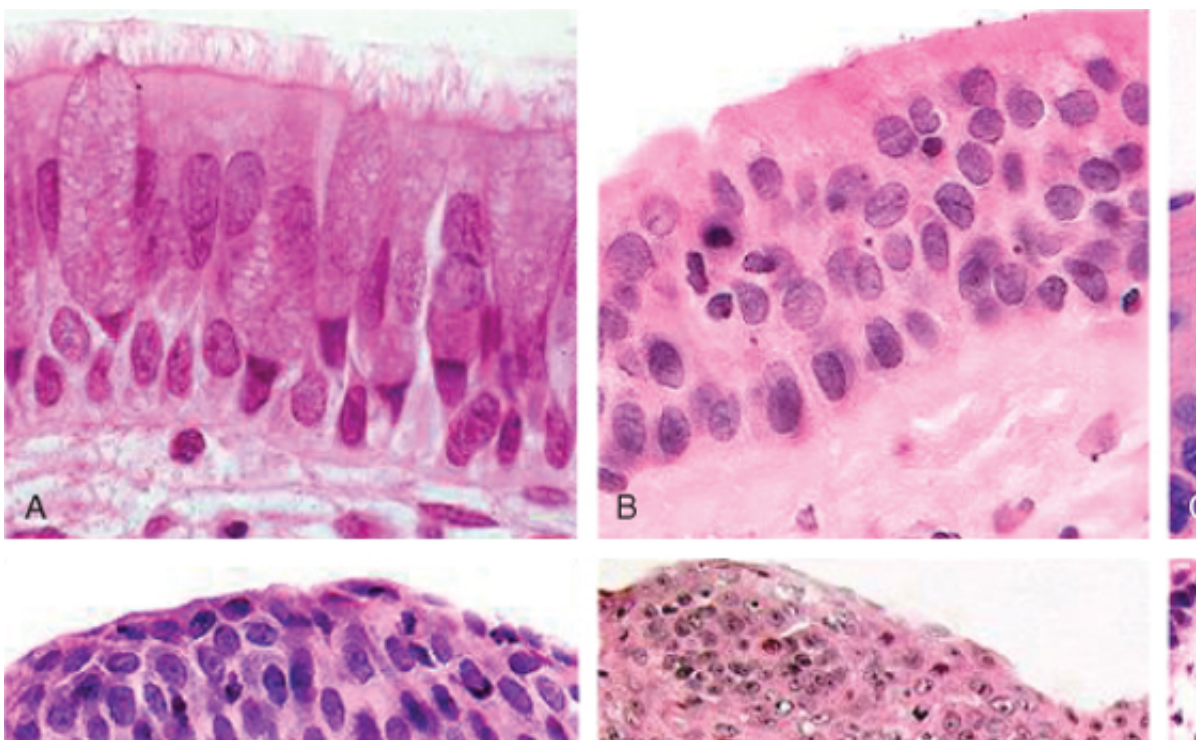
**Large-cell carcinomas** are undifferentiated malignant epithelial tumors that lack tl small-cell carcinoma and glandular or squamous differentiation. The cells typically prominent nucleoli, and a moderate amount of cytoplasm. Large-cell carcinomas p

squamous cell or adenocarcinomas that are so undifferentiated that they can no longer be identified by light microscopy. Ultrastructurally, however, minimal glandular or squamous differentiation can be seen.

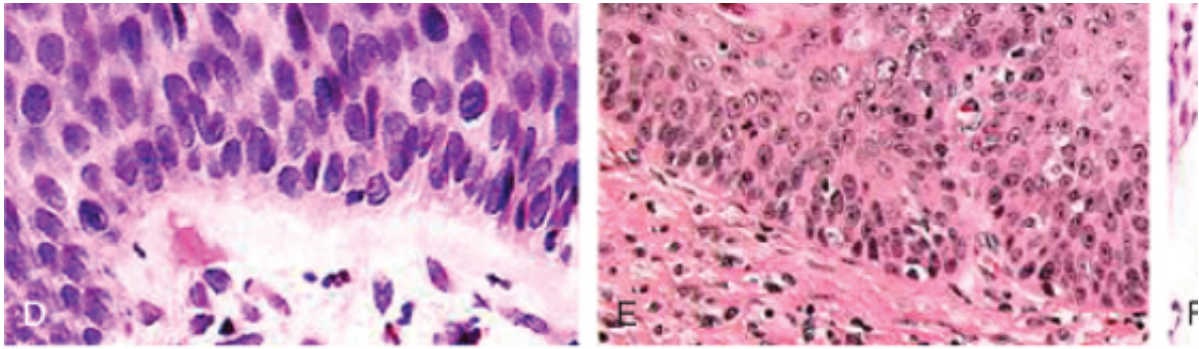
**Small-cell lung carcinomas** generally appear as pale gray, **centrally located** masses within the lung parenchyma and early involvement of the hilar and mediastinal nodes. The tumor is composed of tumor cells with a round to fusiform shape, scant cytoplasm, and finely granular chromatin. These cells are frequently seen (Fig. 13-47A). Despite the appellation of "small," the neoplastic cells are the same size as resting lymphocytes. Necrosis is invariably present and may be extensive. The tumor cells are markedly fragile and often show fragmentation and "crush artifact" in small biopsy specimens. A characteristic feature of small-cell carcinomas, best appreciated in cytologic specimens, is nuclear molding or close apposition of tumor cells that have scant cytoplasm (Fig. 13-47B). These tumors are neuroendocrine cells of the lung, and hence they express a variety of neuroendocrine markers (Fig. 13-9) in addition to a host of polypeptide hormones that may result in paraneoplastic syndromes.

**Combined patterns** require no further comment, but it should be noted that a significant number of bronchogenic carcinomas reveal more than one line of differentiation, sometimes suggesting that all are derived from a multipotential progenitor cell.

For all of these neoplasms, one can trace involvement of successive chains of nodes in the lung, mediastinum, and in the neck (scalene nodes) and clavicular regions and, sooner or later, distant metastases. Involvement of the left supraclavicular node (Virchow node) is particularly significant and sometimes calls attention to an occult primary tumor. These cancers, when advanced, may invade the pericardial or pleural spaces, leading to inflammation and effusions. They may compress the superior vena cava to cause either venous congestion or the full-blown vena caval syndrome. Apical neoplasms may invade the brachial or cervical sympathetic plexus to cause pain, numbness, or distribution of the ulnar nerve or to produce Horner syndrome (ipsilateral enophthalmos, miosis, and anhidrosis). Such apical neoplasms are sometimes called **Pancoast tumors**, and the clinical findings is known as Pancoast syndrome. Pancoast tumor is often accompanied by destruction of the first and second ribs and sometimes thoracic vertebrae. As with other cancers, tumor-node-metastasis categories have been established to indicate the size and spread of the primary neoplasm.

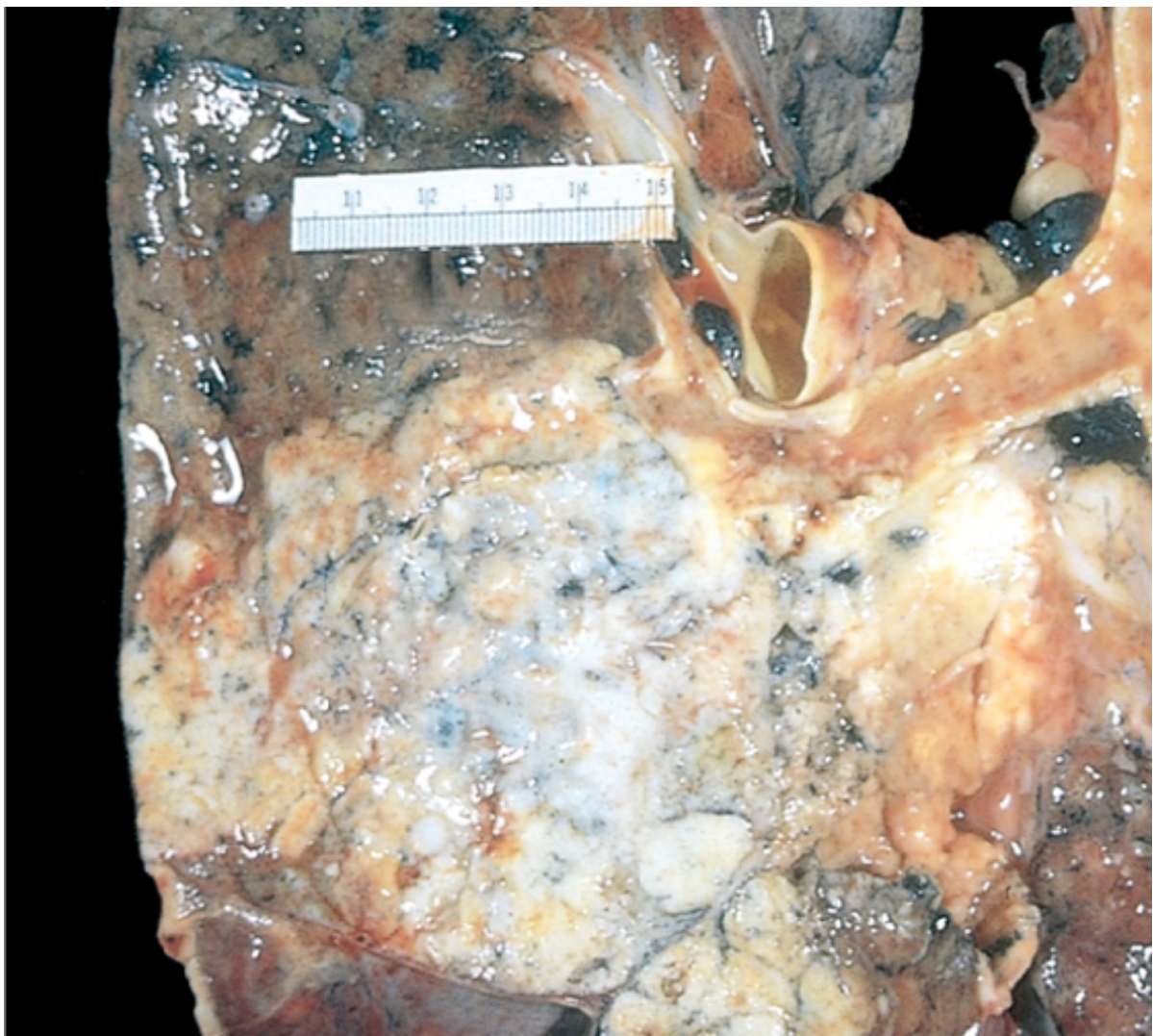






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Figure 13-44 The precursor lesions of squamous cell carcinomas may antedate the appearance of invasive tumor. Changes in smoking-damaged respiratory epithelium include goblet cell hyperplasia (A), basal cell (or reserve cell) hyperplasia, and loss of polarity. More ominous changes include the appearance of squamous dysplasia (D), characterized by the presence of disorganized epithelium, nuclear hyperchromasia, pleomorphism, and mitotic figures. Squamous dysplasia may, in turn, progress to carcinoma-in-situ (CIS) (E), which is the stage that immediately precedes invasive squamous carcinoma (F). In CIS, the cytologic features are similar to those in frank carcinoma. Unless treated, CIS will eventually progress to invasive carcinoma. F, reproduced with permission from the International Agency for Research on Cancer, International Union Against Cancer, World Health Organization Histological Typing of Lung and Pleural Tumors. Heidelberg,



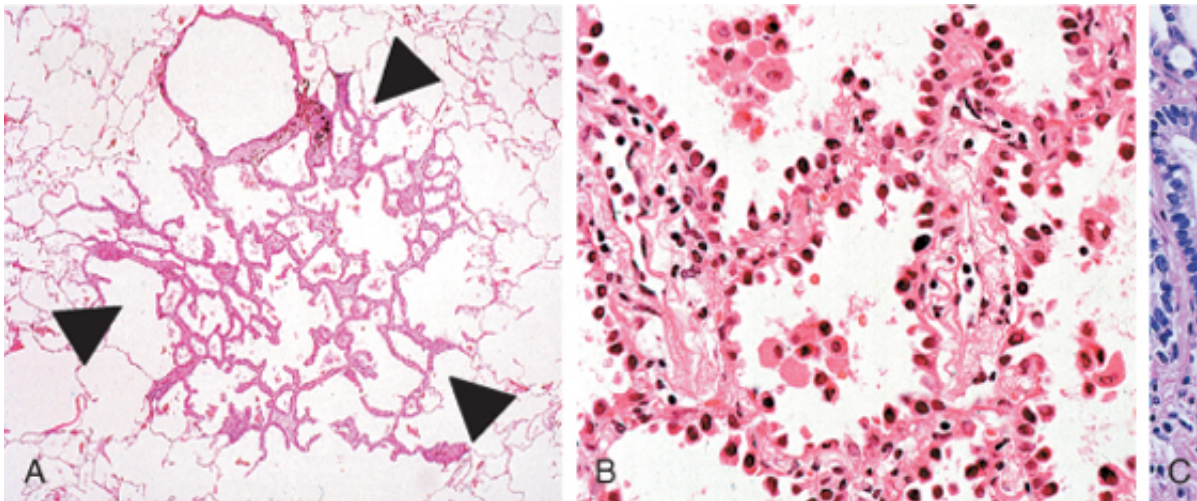




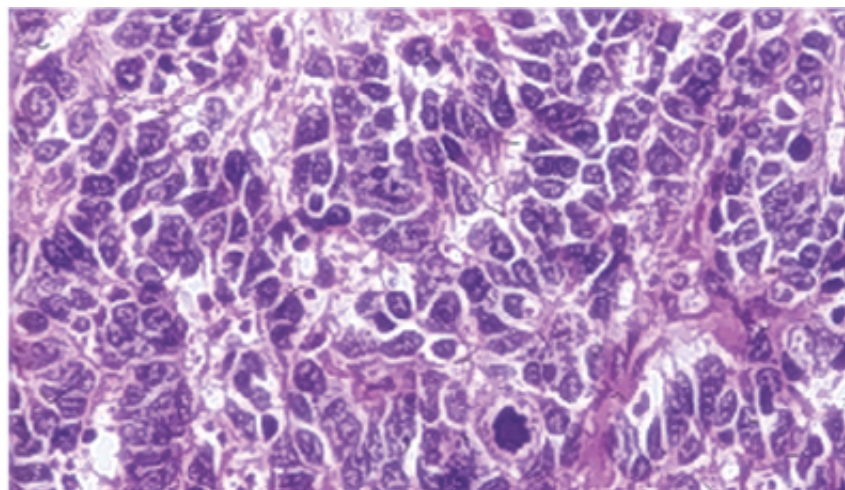
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 Figure 13-45 Squamous cell carcinomas usually begin as central (hilar) masses and grow contiguously into the periphery. Squamous cell carcinomas may undergo cavitory necrosis during intrapulmonary growth.

### Clinical Course

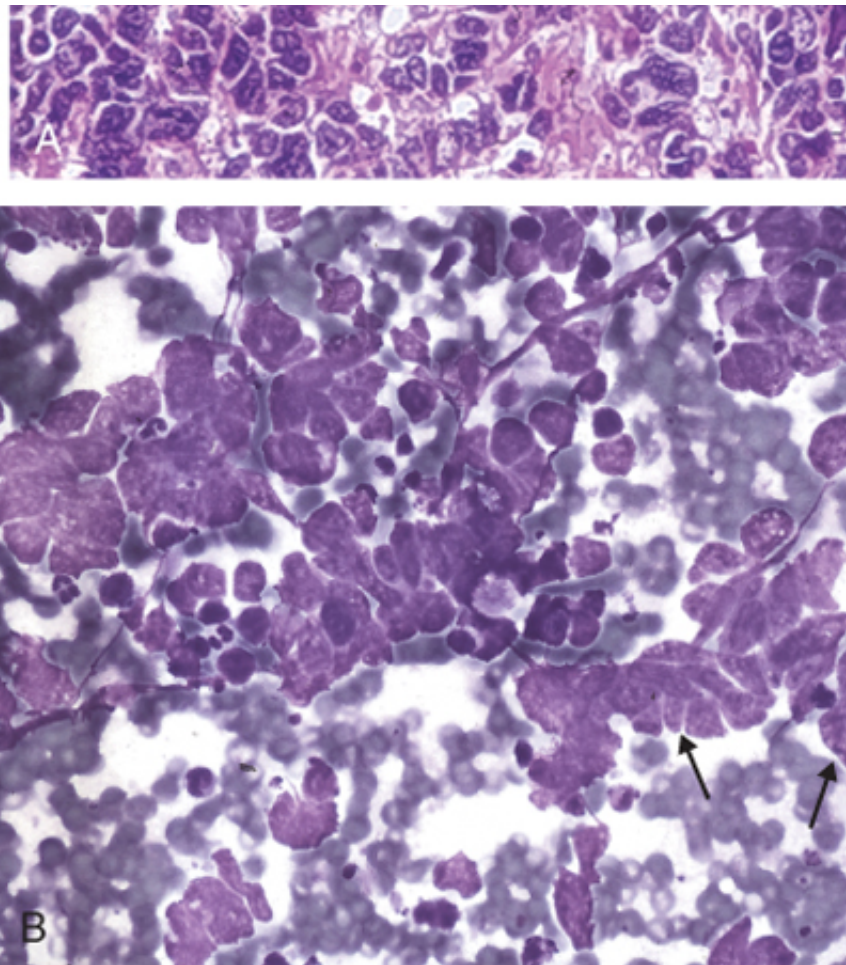
Carcinomas of the lung are silent, insidious lesions that more often than not have spread so as to cause symptoms. In some instances, chronic cough and expectoration call attention to still localized, resectable tumors. In other instances, chest pain, superior vena caval syndrome, pericardial or pleural effusion, or persistent segmental atelectasis, the prognosis is grim. Too often, the tumor presents with symptoms emanating from distant sites (e.g., neurologic changes, liver (hepatomegaly), or bones (pain). Although the adrenals may be nearly normal, adrenal insufficiency (Addison disease) is uncommon because islands of cortical cells sufficient to maintain function are usually present.



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 Figure 13-46 Glandular lesions of the lung. **A**, The putative precursor lesion of invasive adenocarcinoma is the karyophilic micropapillary pattern (arrowheads), which presents typically as multifocal nodules. **B**, Bronchioloalveolar carcinomas are a variant of adenocarcinoma and do not demonstrate evidence of stromal, vascular, or pleural invasion. **C**, Invasive adenocarcinoma, with stromal, vascular, or pleural invasion. Travis WD, et al [eds]: World Health Organization Histological Typing of Lung and Pleural Tumors. Heidelberg, Springer-Verlag, 1999, p 134. Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.







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 Figure 13-47 Small-cell lung carcinoma. **A**, Nests and cords of round to polygonal cells with scant cytoplasm, granular nuclei, and a mitotic figure in center. **B**, Cytologic preparation from a case of small-cell carcinoma demonstrating "nuclear molding" feature in bronchioloalveolar lavage samples or fine-needle aspiration specimens for diagnosis.

Overall, NSCLCs have a better prognosis than SCLCs. When NSCLCs (squamous cell carcinoma) are detected before metastasis or local spread, cure is possible by lobectomy or pneumonectomy. SCLCs, on the other hand, are often detected at a late stage, even if the primary tumor appears small and localized. Thus, surgery is often not curative. They are very sensitive to chemotherapy but invariably recur. Median survival even with treatment is about 12 months.

It is variously estimated that 3% to 10% of all patients with lung cancer develop clinically overt paraneoplastic syndromes. These include: (1) hypercalcemia caused by secretion of a parathyroid hormone-related peptide (osteolytic lesions); (2) Cushing syndrome (from increased production of ACTH); (3) syndrome of inappropriate secretion of antidiuretic hormone; (4) neuromuscular syndromes, including peripheral neuropathy, and polymyositis; (5) clubbing of the fingers and hypertrophic pulmonary osteoarthropathy. Manifestations, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation, have also been documented by assays, but these products are not hormones. Hypercalcemia is most often encountered with squamous cell neoplasms, the hematologic syndromes are more common with small-cell neoplasms, but exceptions abound.

## SUMMARY

**Carcinomas of the Lung** The four major histologic subtypes are adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and small-cell carcinoma (SCLC). The first three are designated as non-small-cell lung cancer (NSCLC). SCLC and NSCLC

genetically distinct. SCLC are best treated by chemotherapy because all are presentation. NSCLCs, by contrast, are curable by surgery (if limited to the important risk factor for lung cancer; adenocarcinomas are most common in and nonsmokers. Precursor lesions include squamous dysplasia (for squamous adenomatous hyperplasia (for some adenocarcinomas). Bronchioloalveolar of adenocarcinomas characterized by absence of stromal invasion and growth structures. Lung cancers, particularly SCLCs, can cause *paraneoplastic syn*

## Bronchial Carcinoids

Bronchial carcinoids are thought to arise from the Kulchitsky cells (neuroendocrine cells) that line intestinal carcinoids ([Chapter 15](#)). The neoplastic cells contain dense-core neurosecretory granules and secrete hormonally active polypeptides. They occasionally occur as part of the multiple endocrine disorder. Bronchial carcinoids appear at an early age (mean 40 years) and represent about 5% of all pulmonary tumors. Unlike their more ominous neuroendocrine counterpart, small-cell carcinomas, carcinoids are often resected.

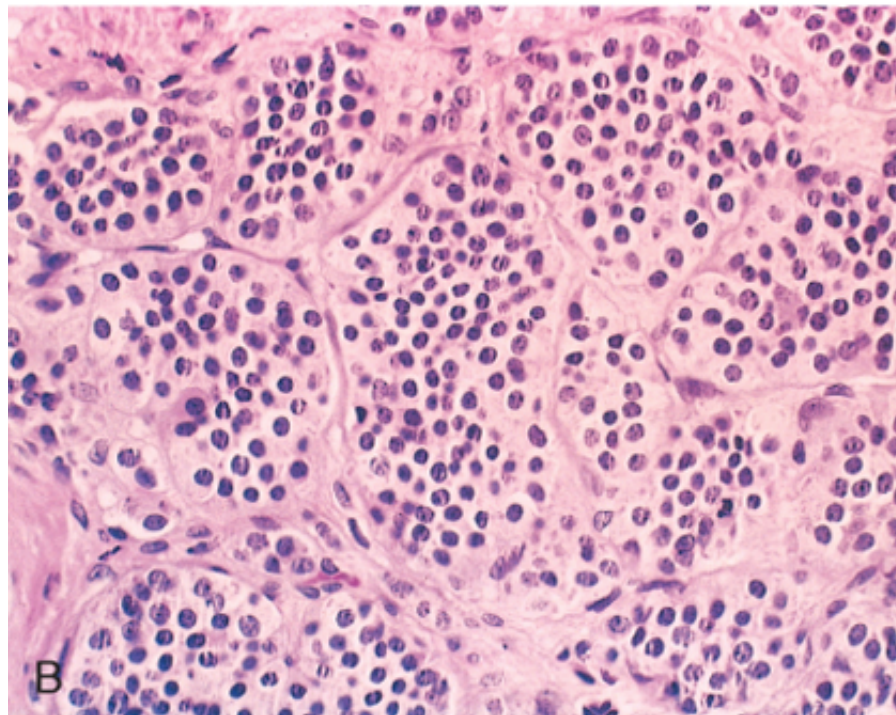
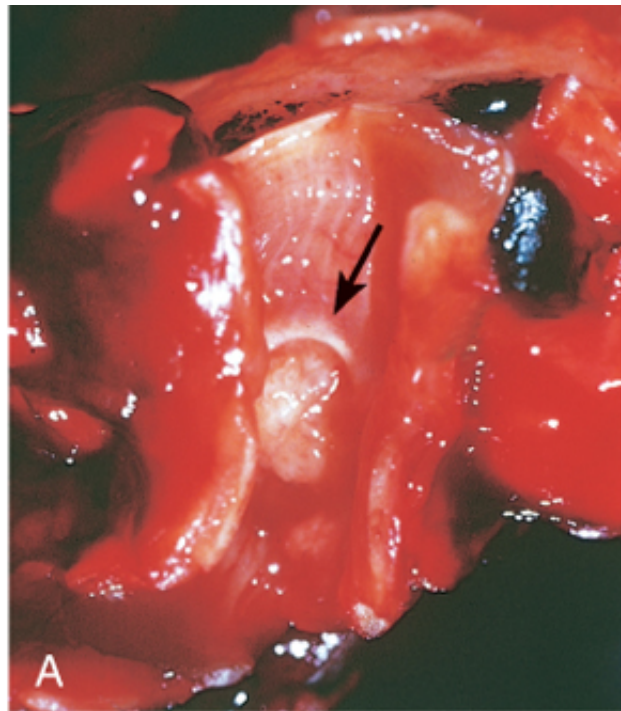
### Morphology

Most bronchial carcinoids originate in main-stem bronchi and grow in one of two patterns: (1) a polypoid, spherical, intraluminal mass ([Fig. 13-48A](#)); or (2) a mucosal plaque that can fan out in the peribronchial tissue-the so-called collar-button lesion. Even these peripheral lesions can extend into the lung substance along a broad front and are therefore reasonably well demarcated from the surrounding lung. At presentation, distant metastases are rare. Most of these tumors have metastasized to the hilar nodes at presentation, distant metastases are rare. Histologically, these neoplasms, like their counterparts in the intestinal tract, are composed of uniform cells that have regular round nuclei with "salt-and-pepper" chromatin, absent mitoses, and little pleomorphism ([Fig. 13-48B](#)). Occasional tumors display a higher mitotic rate, increased cellular variability, and focal necrosis-features that qualify for a designation of **atypical carcinoid**. Persons with atypical carcinoids fare worse in the long run. Unlike typical carcinoids, atypical carcinoids demonstrate *p53* mutations in 20% to 40% of cases. **Typical carcinoid, atypical carcinoid, and small-cell carcinoma can be considered to represent a continuum of increasing histologic malignant potential within the spectrum of pulmonary neuroendocrine neoplasms.**

Most bronchial carcinoids present with findings related to their intraluminal growth (i.e., they cause bronchial and pulmonary infections). Some are asymptomatic and discovered by chance on chest x-ray. The *carcinoid syndrome*, characterized by intermittent attacks of diarrhea, flushing, and cyanosis, is present in about 10% of typical carcinoids, while it drops to 56% and 35%, respectively for atypical carcinoid and small-cell carcinoma. The 5-year survival rate for aggressive neuroendocrine lung tumor-SCLC-is alive at 10 years.



## PLEURAL LESIONS



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Figure 13-48 A, Bronchial carcinoid growing as a spherical, pale mass (arrow) protruding into the lumen of the bi

carcinoid demonstrating small, rounded, uniform cells.

Pathologic involvement of the pleura is, with rare exceptions, a secondary complication of some of the above infections and pleural adhesions are particularly common findings at autopsy. Important primary diseases are (1) bacterial infections and (2) a primary neoplasm of the pleura known as *malignant mesothelioma*.

### **Pleural Effusion and Pleuritis**

Pleural effusion, the presence of fluid in the pleural space, can be either a transudate or an exudate. Transudate is termed *hydrothorax*. Hydrothorax from CHF is probably the most common cause of fluid in the pleural space. Exudate is defined by protein content  $>2.9\text{gm/dL}$  and, often, inflammatory cells, suggests pleuritis. The four principal causes of exudative pleural effusions are: (1) microbial invasion through either direct extension of a pulmonary infection or blood-borne seeding (bacterial, fungal, viral pleuritis); (2) cancer (bronchogenic carcinoma, metastatic neoplasms to the lung or pleural surface, mesothelioma); (3) systemic lupus erythematosus; and (4) previous thoracic surgery. Cancer should be suspected as the underlying cause of an exudative pleural effusion in a patient age of 40, particularly when there is no febrile illness, no pain, and a negative tuberculin test result. Exudative pleural effusions are large and frequently are bloody (*hemorrhagic pleuritis*). Cytologic examination may reveal malignant cells.

Whatever the cause, transudates and serous exudates are usually resorbed without residual effect. In contrast, fibrinous, hemorrhagic, and suppurative exudates may lead to fibrous organization, pleural thickening, and sometimes minimal to massive calcifications.

### **Pneumothorax, Hemothorax, and Chylothorax**

*Pneumothorax* refers to air or other gas in the pleural sac. It may occur in young, apparently healthy individuals without pulmonary disease (simple or spontaneous pneumothorax), or as a result of some thoracic or lung disease such as emphysema or a fractured rib. Secondary pneumothorax occurs with rupture of any pulmonary lesion on the pleural surface that allows inspired air to gain access to the pleural cavity. Such pulmonary lesions include tuberculosis, carcinoma, and many other, less common, processes. Mechanical ventilatory support may also cause a secondary pneumothorax.

There are several possible complications of pneumothorax. A ball-valve leak may create a tension pneumothorax. Compromise of the pulmonary circulation may follow and may even be fatal. If the leak is not corrected within a few weeks (either spontaneously or through medical or surgical intervention), so much serous fluid collects in the pleural cavity and creates hydro-pneumothorax that the lung becomes vulnerable to infection, as does the pleural cavity when communication between it and the lung is lost. This is an important complication of pneumothorax (pyopneumothorax). Secondary pneumothorax tends to recur. What is less well recognized is that simple pneumothorax is also recurrent.

*Hemothorax*, the collection of whole blood (in contrast to bloody effusion) in the pleural cavity, is a complication of aortic aneurysm that is almost always fatal. With hemothorax, in contrast to bloody pleural effusion, the blood is in the pleural cavity.

*Chylothorax* is a pleural collection of a milky lymphatic fluid containing microglobules of lipid. The chylothorax is always significant because it implies obstruction of the major lymph ducts, usually the thoracic duct or secondary mediastinal neoplasm, such as a lymphoma).

### **Malignant Mesothelioma**

Malignant mesothelioma is a rare cancer of mesothelial cells, usually arising in the parietal or visceral pleura, but less commonly, in the peritoneum and pericardium. It has assumed great importance because it is associated with exposure to asbestos in the air. Approximately 50% of individuals with this cancer have a history of exposure to asbestos (shipyard workers, miners, insulators) are at greatest risk, but malignant mesotheliomas have also been reported in individuals whose exposure was living in proximity to an asbestos factory or being a relative of an asbestos worker. The latency period for malignant mesotheliomas is long, often 25 to 40 years after initial asbestos exposure, suggesting a long time required for tumorigenic conversion of a mesothelial cell. As stated earlier, *the combination of cigarette smoking and asbestos exposure greatly increases the risk of bronchogenic carcinoma, but it does not increase the risk of developing malignant mesothelioma*.



### Morphology

Malignant mesotheliomas are often preceded by extensive **pleural fibrosis and pleural thickening**, which is often seen in computed tomographic scans. These tumors begin in a localized area and spread widely, either by contiguous growth or by diffusely seeding the pleural surface. The tumor on the affected lung is **typically ensheathed by a yellow-white, firm, sometimes gelatinous rind** that obliterates the pleural space (Fig. 13-49). Distant metastases are rare. The neoplasm may involve the thoracic wall or the subpleural lung tissue. Normal mesothelial cells are biphasic, consisting of epithelial cells as well as the underlying fibrous tissue. Therefore, histologically, mesothelioma shows three patterns: (1) **epithelial**, in which cuboidal cells line tubular and microcystic spaces; (2) **sarcomatoid**, in which spindled and sometimes fibroblastic cells grow in nondistinctive sheets; and (3) **biphasic**, having both sarcomatoid and epithelial



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Figure 13-49 Malignant mesothelioma. Note the thick, firm, white, pleural tumor that ensheathes the lung.

The basis for the carcinogenicity of asbestos is still a mystery. Asbestos is not removed or metabolized and remains in the body for life. Thus, there is a lifetime risk after exposure that does not diminish with time (the risk decreases after cessation). It has been hypothesized that asbestos fibers preferentially gather near the nucleus and generate reactive oxygen species that cause DNA damage and potentially oncogenic mutations. Several tumor suppressor genes (*p16/CDKN2A* on chromosome 9p21 and *NF2* on chromosome 22q12) have been found to be mutated in mesotheliomas. Recent work has demonstrated the presence of simian virus 40 viral DNA sequences in a subset of mesotheliomas and in a smaller fraction of peritoneal cases. The simian virus 40 T-antigen is a protein that inactivates several essential regulators of growth, such as p53 and RB. Not everyone is convinced that asbestos is a carcinogen; currently, the interaction of asbestos and simian virus 40 in mesothelioma pathogenesis is an area of active research.



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## LESIONS OF THE UPPER RESPIRATORY TRACT

### Acute Infections

Acute infections of the upper respiratory tract are among the most common afflictions of humans, "common cold." The clinical features are well known to all: nasal congestion accompanied by watery discharge; sore throat; and a slight increase in temperature that is more pronounced in young children. The most common viruses are rhinoviruses, but coronaviruses, respiratory syncytial viruses, parainfluenza and influenza viruses are also important. Sometimes even group A  $\beta$ -hemolytic streptococci have been implicated. In a significant number of cases, the exact cause cannot be determined; perhaps new viruses will be discovered. Most of these infections occur in the fall and last for a week or less. In a minority of cases, colds may be complicated by the development of

In addition to the common cold, infections of the upper respiratory tract may present as signs and symptoms of epiglottitis, or larynx. *Acute pharyngitis*, manifesting as a sore throat, may be caused by a host of agents. A physical finding frequently accompanies a cold and is the most common form of pharyngitis. More severe forms, with marked hyperemia and exudates, occur with  $\beta$ -hemolytic streptococci and adeno-virus infections. It is important to recognize and treat early, because of its potential to develop peritonsillar abscesses ("quinsy"), glomerulonephritis and acute rheumatic fever. Coxsackievirus A may produce pharyngeal vesicles. Infectious mononucleosis, caused by Epstein-Barr virus (EBV), is an important cause of pharyngitis and bears a reflection on the common mode of transmission in previously nonexposed individuals.

*Acute bacterial epiglottitis* is a syndrome predominantly of young children who have an infection of the larynx. Pain and airway obstruction are the major findings. The onset is abrupt. Failure to appreciate the condition in a child with this condition can be fatal. The advent of vaccination against *H. influenzae* has greatly reduced its incidence.

*Acute laryngitis* can result from inhalation of irritants or may be caused by allergic reactions. It may also produce the common cold and usually involve the pharynx and nasal passages as well as the larynx. Two uncommon but important forms of laryngitis: *tuberculous* and *diphtheritic*. The former is almost always associated with tuberculosis, during which infected sputum is coughed up. Diphtheritic laryngitis has fortunately been almost eliminated by widespread immunization of young children against diphtheria toxin. After it is inhaled, *Corynebacterium diphtheriae* of the upper airways and elaborates a powerful exotoxin that causes necrosis of the mucosa, producing a fibrinopurulent exudate that creates the classic superficial, dirty-gray pseudomembrane of diphtheria. The membrane is sloughing and aspiration of the pseudomembrane (causing obstruction of major airways) and may lead to (producing myocarditis, peripheral neuropathy, or other tissue injury).

In children, parainfluenza virus is the most common cause of laryngotracheobronchitis, more commonly known as croup. Such viruses as respiratory syncytial virus may also precipitate this condition. Although self-limited, croup can be severe and harsh, persistent cough. In occasional cases the laryngeal inflammatory reaction may narrow the airway, leading to respiratory failure. Viral infections in the upper respiratory tract predispose the patient to secondary bacterial infections, such as staphylococci, streptococci, and *H. influenzae*.

### Nasopharyngeal Carcinoma

This rare neoplasm merits comment because of (1) the strong epidemiologic links to EBV and (2) its high incidence in the Chinese, which raises the possibility of viral oncogenesis on a background of genetic susceptibility. The virus replicates in the nasopharyngeal epithelium and then infects nearby tonsillar B lymphocytes. In the process, it transforms the epithelial cells. Unlike the case with Burkitt lymphoma ([Chapter 12](#)), another form of lymphoma is found in virtually all nasopharyngeal carcinomas, including those that occur outside the endemic areas.

The three histologic variants are keratinizing squamous cell carcinoma, nonkeratinizing squamous cell carcinoma; the last-mentioned is the most common and the one most closely linked with EBV. The nonkeratinizing variant is characterized by large epithelial cells having indistinct cell borders ("syncytial" growth) and prominent nucleoli. It is recalled that in infectious mononucleosis, EBV directly infects B lymphocytes, after which a marked

revealed that in infectious mononucleosis, EBV directly infects B lymphocytes, after which a marked atypical lymphocytosis, seen in the peripheral blood, and enlarged lymph nodes (Chapter 10). In carcinomas a striking influx of mature lymphocytes can often be seen. These neoplasms are therefore a misnomer because the lymphocytes are not part of the neoplastic process, nor are the tumor cells in a background of reactive lymphocytes may give rise to an appearance similar to non-Hodgkin's lymphoma. Immunohistochemical stains may be required to prove the epithelial nature of the malignant cells. Locally, spread to cervical lymph nodes, and then metastasize to distant sites. They tend to be radiosensitive. 50% are reported for even advanced cancers.

## Laryngeal Tumors

A variety of non-neoplastic, benign, and malignant neoplasms of squamous epithelial and mesenchymal origin. Only vocal cord nodules, papillomas, and squamous cell carcinomas are sufficiently common to mention. The most common presenting feature is hoarseness.

### Nonmalignant Lesions

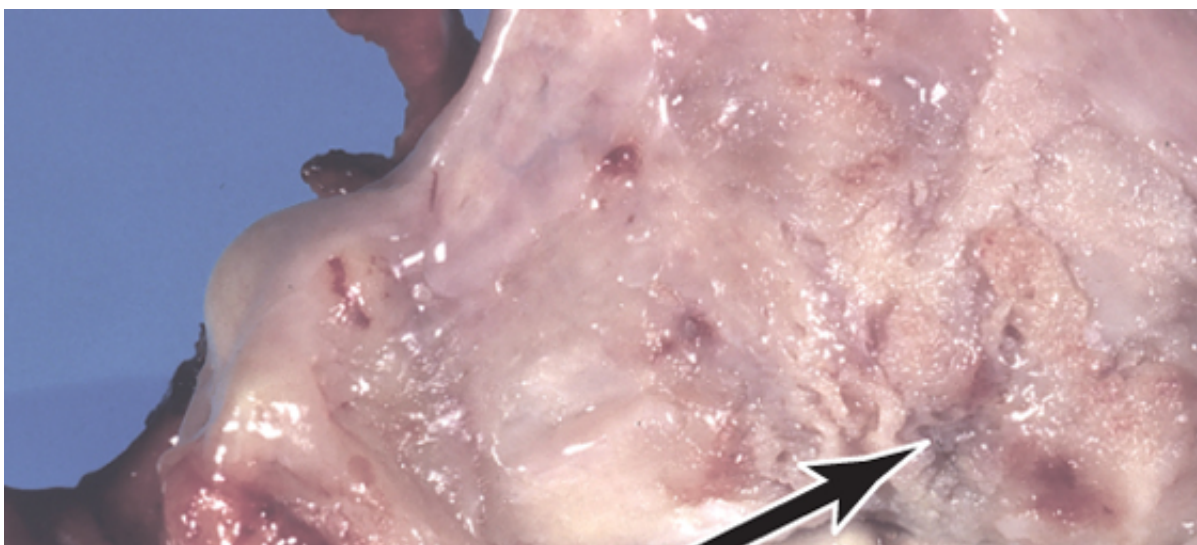
*Vocal cord nodules* ("polyps") are smooth, hemispherical protrusions (usually less than 0.5 cm in diameter) on the vocal cords. The nodules are composed of fibrous tissue and covered by stratified squamous mucosa. They may become ulcerated by contact trauma with the other vocal cord. These lesions occur chiefly in heavy smokers and are the result of chronic irritation or abuse.

*Laryngeal papilloma* or *squamous papilloma* of the larynx is a benign neoplasm, usually on the true vocal cord. It is a raspberry-like excrescence rarely more than 1 cm in diameter. Histologically, it consists of multiple finger-like projections supported by central fibrovascular cores and covered by an orderly, typical, stratified squamous epithelium. On the free edge of the vocal cord, trauma may lead to ulceration that can be accompanied by hemoptysis.

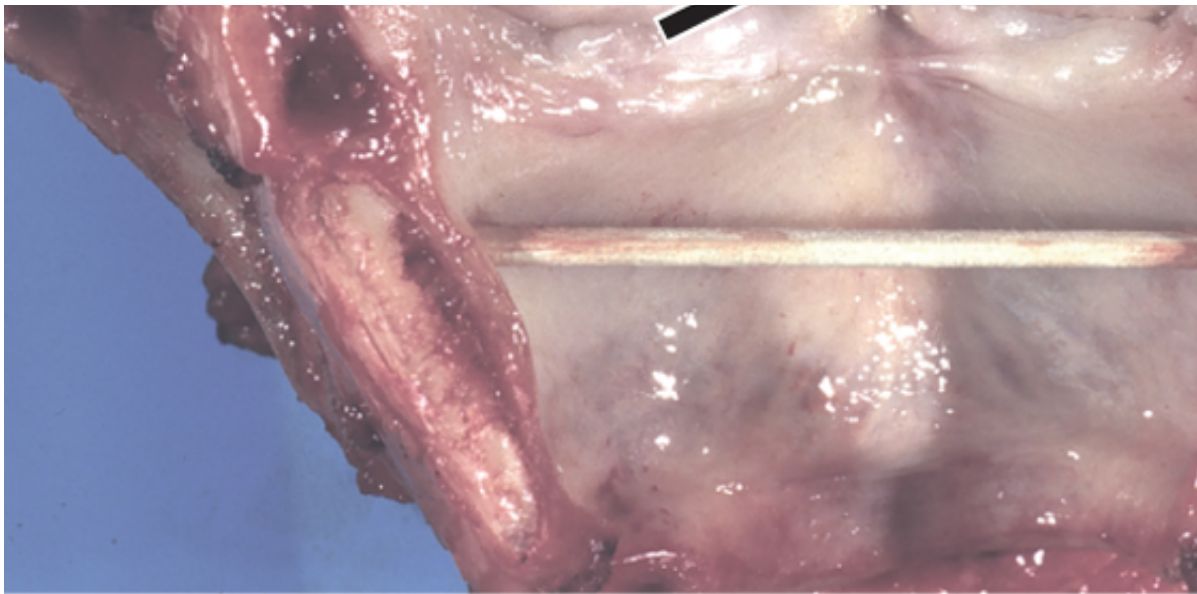
Papillomas are usually single in adults but are often multiple in children, in whom they are referred to as *recurrent respiratory papillomatosis* (RRP), since they typically tend to recur after excision. These lesions are caused by human papillomavirus (HPV) types 6 and 11, do not become malignant, and often spontaneously regress at puberty. Cancerous transformation of RRP is rare. Their occurrence in children is believed to be vertical transmission from an infected mother during delivery. In adults, their occurrence is believed to be related to HPV infection. An HPV vaccine that can protect women in the reproductive age group against types 6 and 11 is available. It is important to prevent RRP in children.

### Carcinoma of the Larynx

Carcinoma of the larynx represents only 2% of all cancers. It most commonly occurs after age 40 and is more common in men than in women. Environmental influences are very important in its causation; nearly all cases occur in smokers. Alcohol exposure may also play a role.







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Figure 13-50 Laryngeal squamous cell carcinoma (arrow) arising in a supraglottic location (e

About 95% of laryngeal carcinomas are typical squamous cell lesions. Rarely, adenocarcinomas or mucous glands. The tumor develops directly on the vocal cords (glottic tumors) in 60% to 75% of (supraglottic; 25% to 40%) or below the cords (subglottic; less than 5%). The major etiologic factors for laryngeal carcinomas include most importantly smoking, but also alcohol and previous radiation exposure. It has been detected in a minority of cases. Squamous cell carcinomas of the larynx follow the growth pattern of squamous cell carcinomas. They begin as in situ lesions that later appear as pearly gray, wrinkled plaques on the mucosal surface (Fig. 13-50). The glottic tumors are usually keratinizing, well- to moderately differentiated squamous cell carcinomas. Nonkeratinizing, poorly differentiated carcinomas may also be seen. As expected with lesions arising from environmental carcinogens, adjacent mucosa may demonstrate squamous cell hyperplasia with foci of dysplasia.

Carcinoma of the larynx manifests itself clinically by persistent hoarseness. The location of the tumor and its bearing on prognosis. For example, about 90% of glottic tumors are confined to the larynx at diagnosis. If the tumor involves the vocal cord mobility, they develop symptoms early in the course of disease; second, the glottic tumors rarely spread beyond the larynx. By contrast, the supraglottic larynx is rich in lymphatics and tumors metastasize to regional (cervical) lymph nodes. The subglottic tumors tend to remain clinically localized. With surgery, radiation, or combined therapeutic treatments, many patients can be cured. The usual cause of death is infection of the distal respiratory passages or widespread metastatic disease.

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## 14 The Kidney and Its Collecting System

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The kidney is a structurally complex organ that has evolved to carry out a number of important functions: excretion of the waste products of metabolism, regulation of body water and salt, maintenance of appropriate acid balance, and secretion of a variety of hormones and autacoids. Diseases of the kidney are as complex as its structure, but their study is facilitated by dividing them into those that affect the four basic morphologic components: glomeruli, tubules, interstitium, and blood vessels. This traditional approach is useful because the early manifestations of diseases that affect each of these components tend to be distinctive. Furthermore, some components seem to be more vulnerable to specific forms of renal injury; for example, glomerular diseases are often immunologically mediated, whereas tubular and interstitial disorders are more likely to be caused by toxic or infectious agents. Nevertheless, some disorders affect more than one structure. In addition, the anatomic interdependence of structures in the kidney implies that damage to one almost always secondarily affects the others. Thus, severe glomerular damage impairs the flow through the peritubular vascular system; conversely, tubular destruction, by increasing intraglomerular pressure and inducing cytokines and chemokines, may induce glomerular sclerosis. Whatever the origin, there is a tendency for all forms of chronic renal disease ultimately to damage all four components of the kidney, culminating in chronic renal failure and what has been called *end-stage kidney disease*. The functional reserve of the kidney is large, and much damage may occur before functional impairment is evident. For these reasons, the early signs and symptoms of renal disease are particularly important to the clinician, and these are referred to in the discussion of individual diseases.



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## CLINICAL MANIFESTATIONS OF RENAL DISEASES

The clinical manifestations of renal disease can be grouped into reasonably well-defined syndromes. Some are peculiar to glomerular diseases; others are present in diseases that affect any one of the components. Before we list the syndromes, a few terms must be clarified.

*Azotemia* refers to an elevation of blood [urea](#)<sup>®</sup>, nitrogen and creatinine levels and is largely related to a decreased glomerular filtration rate (GFR). Azotemia is produced by many renal disorders, but it also arises from extrarenal disorders. *Prerenal azotemia* is encountered when there is hypoperfusion of the kidneys, which decreases GFR *in the absence of parenchymal damage*. *Postrenal azotemia* can result when urine flow is obstructed below the level of the kidney. Relief of the obstruction is followed by correction of the azotemia.

When azotemia progresses to clinical manifestations and systemic biochemical abnormalities, it is termed *uremia*. Uremia is characterized not only by failure of renal excretory function but also by a host of metabolic and endocrine alterations incident to renal damage. There is, in addition, secondary gastrointestinal (e.g., uremic gastroenteritis), neuromuscular (e.g., peripheral neuropathy), and cardiovascular (e.g., uremic fibrinous pericarditis) involvement.

We can now turn to a brief description of the major renal syndromes:

1. *Acute nephritic syndrome* is a glomerular syndrome dominated by the acute onset of usually grossly visible hematuria (red blood cells in urine), mild to moderate proteinuria, azotemia, edema, and hypertension; it is the classic presentation of acute poststreptococcal glomerulonephritis.
2. The *nephrotic syndrome* is a glomerular syndrome characterized by heavy proteinuria (excretion of >3.5 gm of protein/day in adults), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria (lipid in the urine).
3. *Asymptomatic hematuria or proteinuria*, or a combination of these two, is usually a manifestation of subtle or mild glomerular abnormalities.
4. *Rapidly progressive glomerulonephritis* results in loss of renal function in a few days or weeks and is manifested by microscopic hematuria, dysmorphic red blood cells and red blood cell casts in the urine sediment, and mild-to-moderate proteinuria.
5. *Acute renal failure* is dominated by oliguria or anuria (no urine flow), with recent onset of azotemia. It can result from glomerular injury (such as crescentic glomerulonephritis), interstitial injury, vascular injury (such as thrombotic microangiopathy), or acute tubular necrosis.
6. *Chronic renal failure*, characterized by prolonged symptoms and signs of uremia, is the end result of all chronic renal diseases.
7. *Urinary tract infection* is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic, and it may affect the kidney (*pyelonephritis*) or the bladder (*cystitis*) only.
8. *Nephrolithiasis* (renal stones) is manifested by renal colic, hematuria, and recurrent stone formation.

In addition to these renal syndromes, *urinary tract obstruction* and *renal tumors*, discussed later, represent specific anatomic lesions that often have varied manifestations.

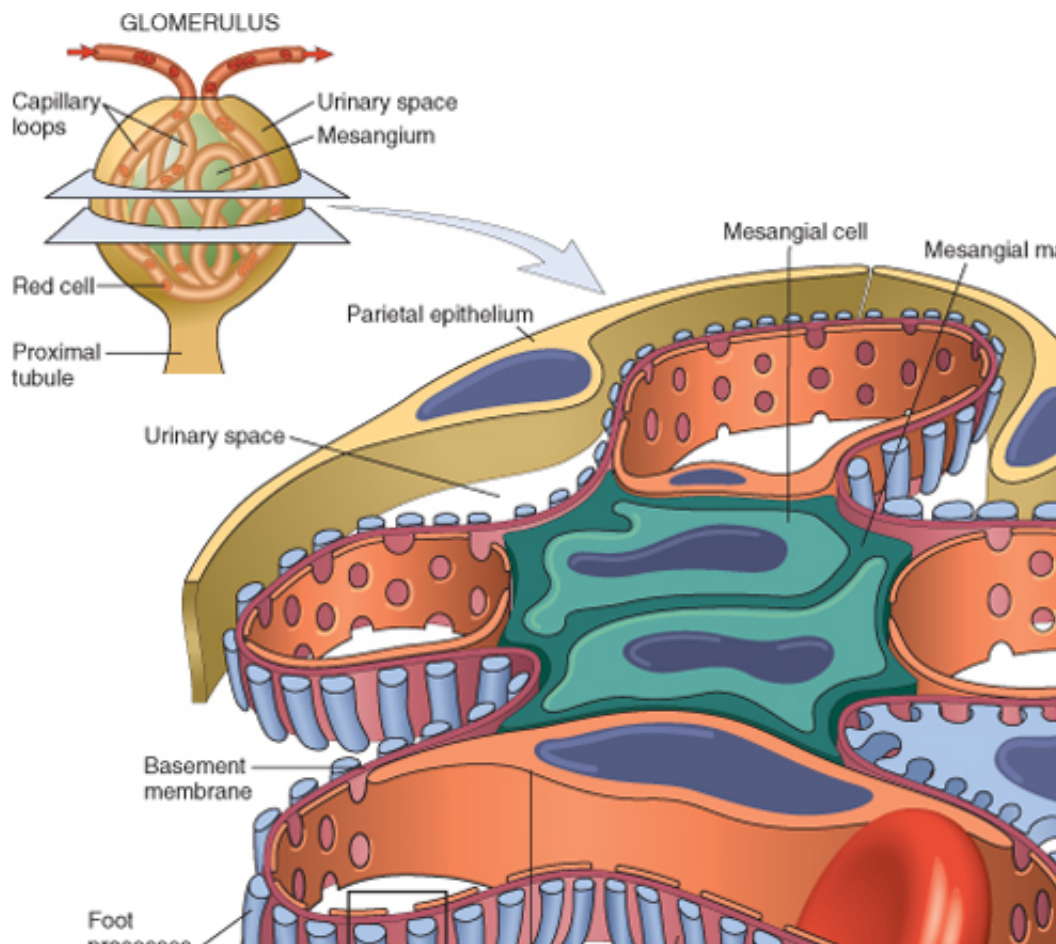


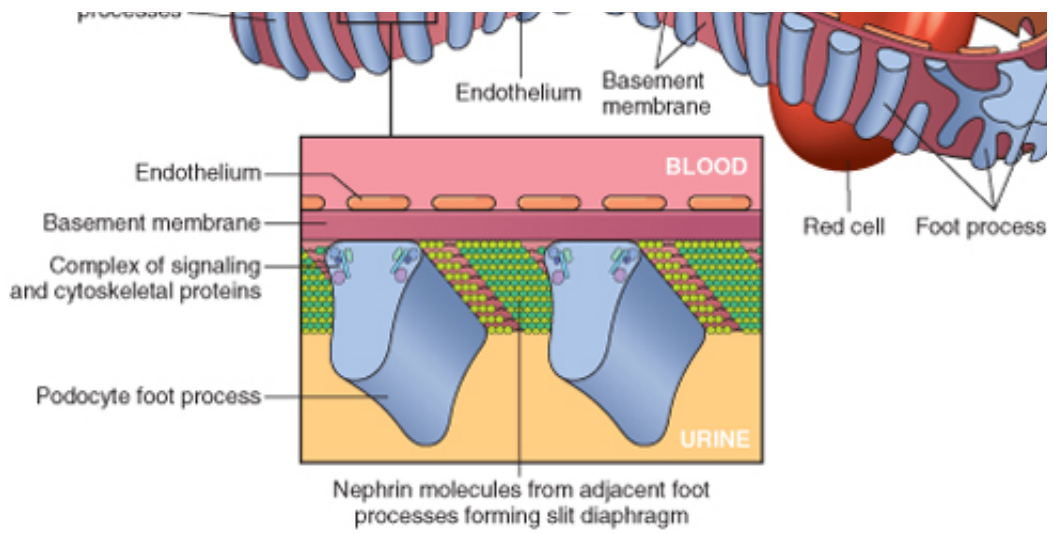


## GLOMERULAR DISEASES

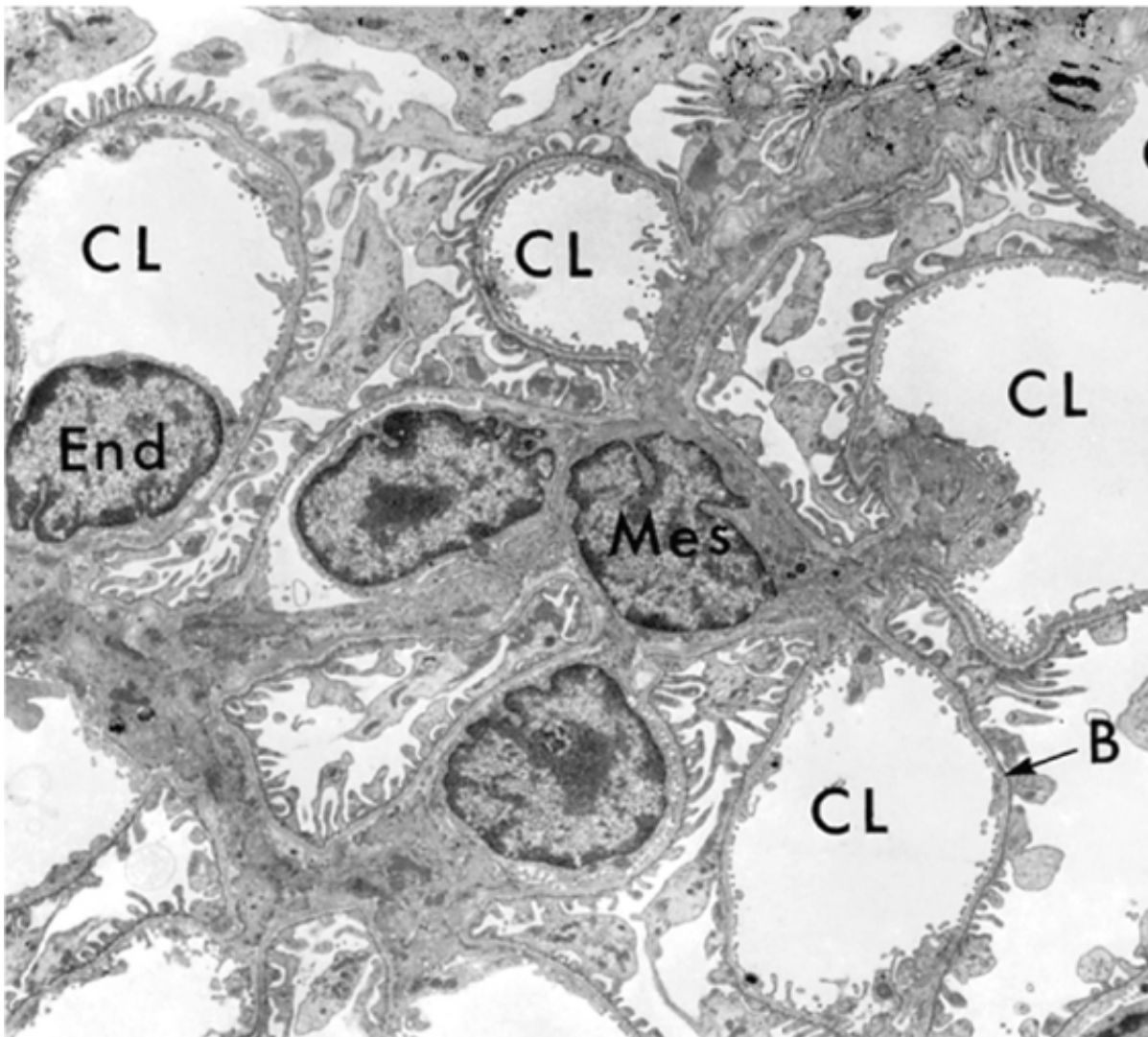
Glomerular diseases constitute some of the major problems encountered in nephrology; indeed, they are among the most common causes of chronic kidney disease in humans. Recall that the glomerulus consists of a tuft of capillaries invested by two layers of epithelium. The visceral epithelium (podocytes) is an intrinsic part of the epithelium lines Bowman space (urinary space), the cavity in which plasma ultrafiltrate first collects. The filtration unit and consists of the following structures (Figs. 14-1 and 14-2):

1. A thin layer of fenestrated *endothelial cells*, each fenestra 70 to 100 nm in diameter.
2. A *glomerular basement membrane* (GBM) with a thick, electron-dense central layer, the *lamina densa*, and two thin peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of copolyanionic proteoglycans, fibronectin, and several other glycoproteins.
3. The *visceral epithelial cells* (podocytes), structurally complex cells that possess interdigitating foot processes to the lamina rara externa of the basement membrane. Adjacent foot processes are separated by narrow slits which are bridged by a thin slit diaphragm composed in large part of nephrin (see below).
4. The entire glomerular tuft is supported by *mesangial cells* lying between the capillaries. These cells form a meshwork through which the mesangial cells are scattered. These cells, of mesenchymal origin, are capable of proliferation, of laying down both matrix and collagen, and of secreting a number of cytokines.





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Figure 14-1 Schematic diagram of a lobe of a normal glomerulus.





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Figure 14-2 Low-power electron micrograph of rat glomerulus. B, basement membrane; CL, capillary lumen; E (podocytes) with foot processes; Mes, mesangium; US, urinary space

The major characteristics of glomerular filtration are an extraordinarily high permeability to water and an impermeability to molecules of the size and molecular charge of albumin (size: 3.6 nm radius; 70,000 Da), called glomerular barrier function, discriminates among protein molecules depending on their size and molecular charge (the more cationic, the more permeable), and their configuration. This size-dependent and charge-dependent permeability is accounted for by the complex structure of the capillary wall, the integrity of the GBM, and the macula densa wall, including the acidic proteoglycans of the GBM and the sialoglycoproteins of epithelial and endothelial cells. A crucial component to the maintenance of glomerular barrier function: its filtration slit diaphragm presents a diffusion barrier to the filtration of proteins, and it is largely responsible for synthesis of GBM components.

In the past few years much has been learned about the molecular architecture of the glomerular filtration barrier. The slit diaphragm transmembrane glycoprotein, is the major component of the slit diaphragms between adjacent foot processes. The slit diaphragm between adjacent foot processes bind to each other through disulfide bridges at the center of the slit diaphragm. The slit diaphragm protein molecules binds to and interacts with several cytoskeletal and signaling proteins (see Fig. 14-1). Nephritic proteins, including *podocin*, have a crucial role in maintaining the selective permeability of the glomerular filtration barrier. Mutations in these proteins, including *podocin*, have a crucial role in maintaining the selective permeability of the glomerular filtration barrier, as illustrated by rare hereditary diseases in which mutations of nephrin or its partner proteins are associated with proteinuria. These proteins, giving rise to the nephrotic syndrome (discussed below). This suggests that acquired defects in the slit diaphragm may constitute an important mechanism of proteinuria, which is the hallmark of the nephrotic syndrome.

Table 14-1. Glomerular Diseases

<b>Primary Glomerular Diseases</b>
Minimal-change disease
Focal and segmental glomerulosclerosis
Membranous nephropathy
Acute postinfectious GN
Membranoproliferative GN
IgA nephropathy
Chronic GN
<b>Glomerulopathies Secondary to Systemic Diseases</b>
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
GN secondary to lymphoplasma-cytic disorders
Goodpasture syndrome
Microscopic polyangiitis
Wegener's granulomatosis
Henoch-Schönlein purpura
Bacterial endocarditis-related GN
GN secondary to extrarenal infection
Thrombotic microangiopathy
<b>Hereditary Disorders</b>
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

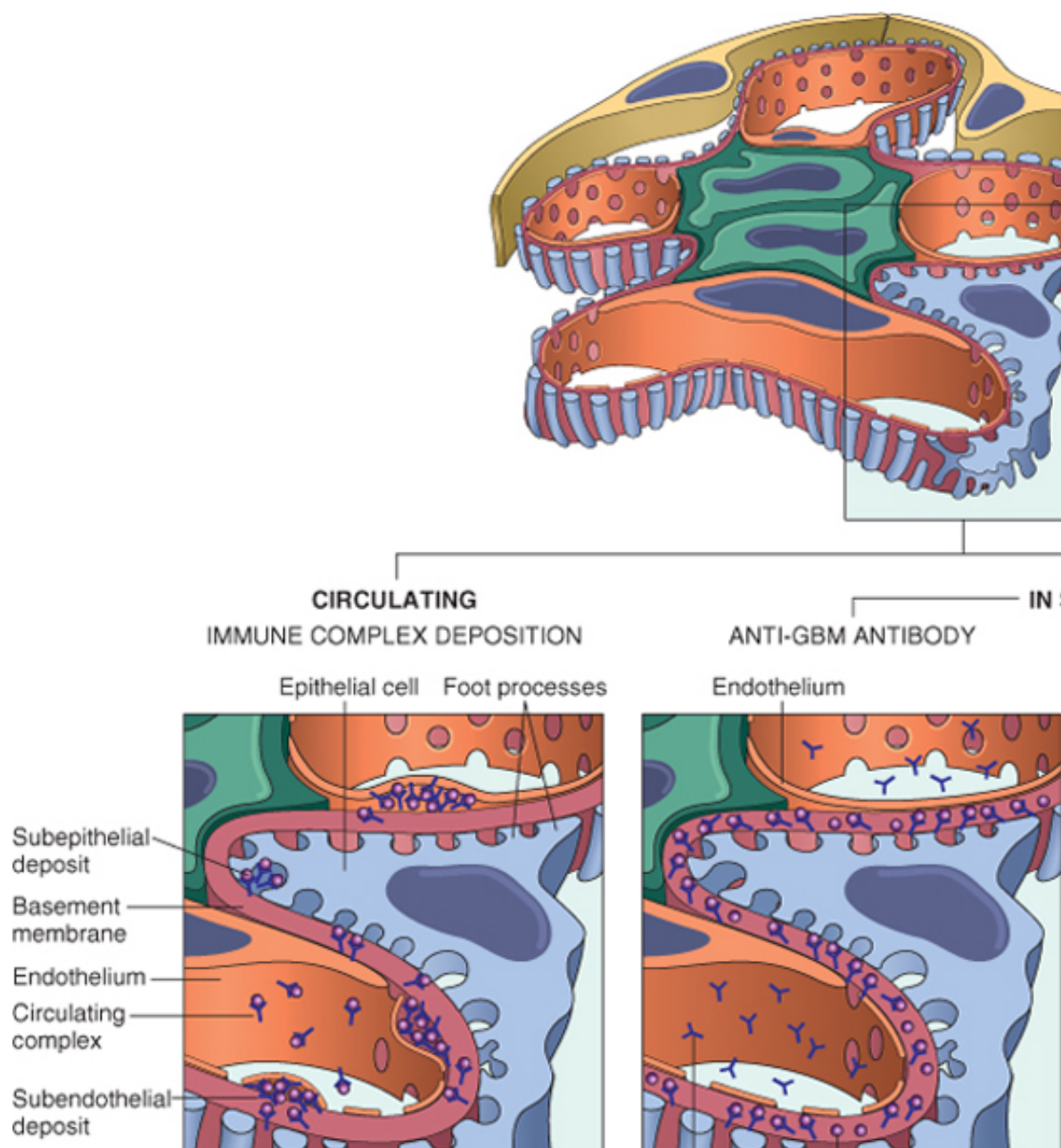
GN, glomerulonephritis.

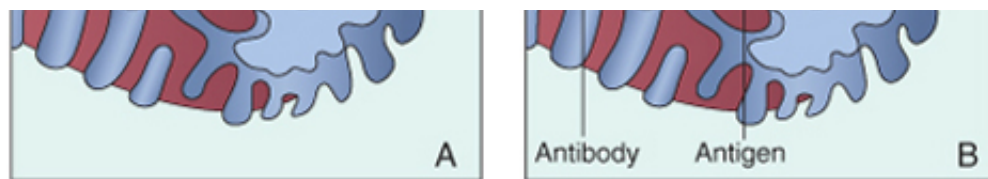


Glomeruli may be injured by diverse mechanisms and in the course of a number of systemic diseases. Immune-mediated diseases such as systemic lupus erythematosus (SLE), vascular disorders such as hypertension, and metabolic diseases such as diabetes mellitus, and some purely hereditary conditions can affect the glomerulus. These are termed *secondary glomerular diseases* to differentiate them from those in which the kidney is the predominant organ involved. The latter constitute the various types of *primary glomerular disease*. The glomerular alterations in systemic diseases are discussed in other parts of this book.

### Pathogenesis of Glomerular Diseases

Although we know little about the etiologic agents or triggering events, it is clear that immune mechanisms are involved in many of the secondary glomerular diseases. Experimentally, GN can be induced by glomerular deposits of immunoglobulins, often with various components of complement, are found in glomerulonephritis. Cell-mediated immune mechanisms may also play a role in certain glomerular





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 Figure 14-3 Antibody-mediated glomerular injury. Injury can result either from the deposition of circulating immune complexes in the glomerulus, or from antibodies reacting in situ within the glomerulus against glomerular antigens or with molecules planted within the glomerulus (Fig. 14-3). In addition, antibodies against some glomerular components may cause glomerular injury. These pathways are not mutually exclusive, and in human disease they often overlap.

Two forms of antibody-associated injury have been established: (1) injury resulting from deposition of immune complexes in the glomerulus, and (2) injury by antibodies reacting in situ within the glomerulus against glomerular antigens or with molecules planted within the glomerulus (Fig. 14-3). In addition, antibodies against some glomerular components may cause glomerular injury. These pathways are not mutually exclusive, and in human disease they often overlap.

### ***Nephritis Caused by Circulating Immune Complexes***

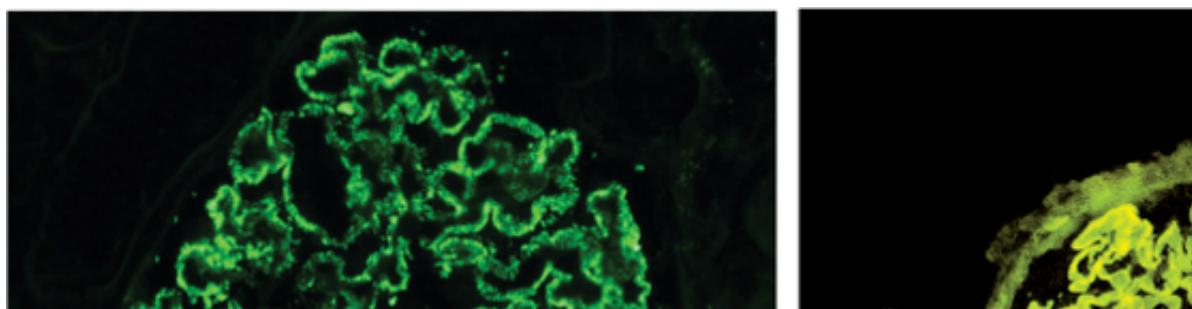
The pathogenesis of immune complex diseases (type III hypersensitivity reactions) was discussed in Chapter 13. In this section, we review the salient features that relate to glomerular injury in glomerulonephritis (GN). With circulating immune complexes, the glomerulus may be considered an "innocent bystander" because it does not incite the reaction. It may be endogenous, as in the GN associated with SLE, or it may be exogenous, as is probable in streptococcal, viral (hepatitis B), parasitic (*Plasmodium falciparum* malaria), and spirochetal (Treponema) infections. In some cases, the inciting antigen is unknown, as in most cases of membranous nephropathy.

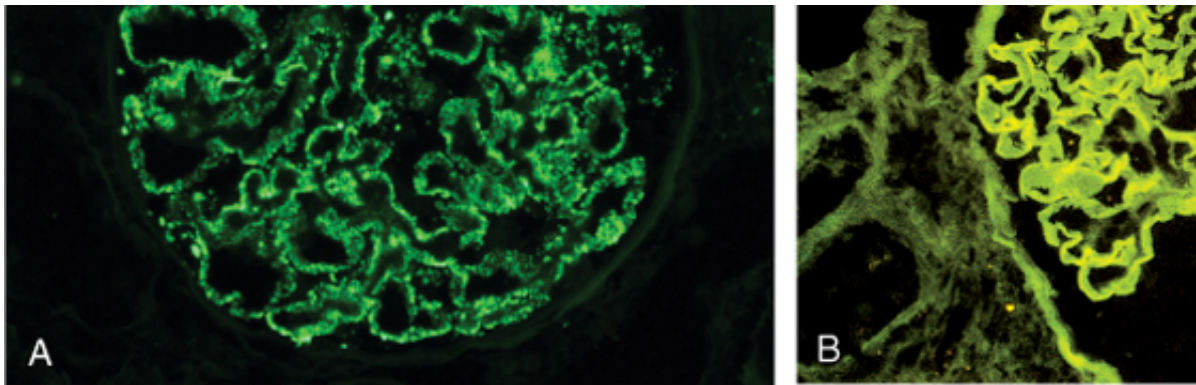
Whatever the antigen may be, antigen-antibody complexes are formed in situ or in the circulation where they produce injury, in large part through the activation of complement and the recruitment of leukocytes through the engagement of Fc receptors on leukocytes independent of complement activation. Renal glomerular lesions usually consist of leukocytic infiltration (exudation) into glomeruli and variable injury to glomerular endothelial and parietal epithelial cells. Electron microscopy reveals the immune complexes as electron-dense deposits in the mesangium, between the endothelial cells and the GBM (subendothelial deposits), or between the endothelial cells and the podocytes (subepithelial deposits). Deposits may be located at more than one site in a given glomerulus. If immunoglobulins and complement in these deposits can be demonstrated by immunofluorescence, the pattern of deposition is helpful in distinguishing various types of GN. When immunoglobulin or anti-complement antibodies are used, the immune complexes are seen as granular deposits (Fig. 14-4A). The pattern of immune complex deposition is helpful in distinguishing various types of GN. Over time, immune complexes may eventually be degraded or phagocytosed, mostly by infiltrating leukocytes and macrophages. Such a course occurs when the exposure to the inciting antigen is short, as in poststreptococcal or acute infection-related GN. However, if the shower of antigens is continuous, formation, deposition, and injury may occur, leading to chronic GN. In some cases the source of circulating antigens is continuous, as in hepatitis B virus infection and self nuclear antigens in SLE. In other cases, however, the anti-

### ***Nephritis Caused by In Situ Immune Complexes***

As noted, antibodies in this form of injury react directly with fixed or planted antigens in the glomerulus.

#### ***Anti-Glomerular Basement Membrane (GBM) Antibody Glomerulonephritis***





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Figure 14-4 Two patterns of deposition of immune complexes as seen by immunofluorescence microscopy. **A**, Granular immune complex deposition. **B**, Linear, characteristic of classic anti-GBM antibody GN. (**A**, Courtesy of Dr. J. Kow Washington, Seattle, Washington.)

The best-characterized disease in this group is classic anti-GBM antibody GN (see Fig. 14-3B). It is directed against fixed antigens in the GBM. It has its experimental counterpart in the nephritis of *rat anti-GBM nephritis*. This is produced by injecting rats with anti-GBM antibodies produced by immunization of rats with *rat anti-GBM antibody GN in humans results from the formation of autoantibodies directed against the basement membrane antigen*. Although in the experimental model anti-GBM antibodies are produced by injecting "foreign" kidney antigens, in humans *anti-GBM antibody GN in humans results from the formation of autoantibodies directed against the basement membrane antigen* creates a *linear pattern* of staining when the bound antibodies are visualized with immunofluorescence. The granular pattern described for other forms of immune complex-mediated nephritis (see Fig. 14-4B) is characteristic of *granular immune complex deposition* in the diagnosis of glomerular disease. The basement membrane antigen responsible for classic anti-GBM antibody GN is the noncollagenous domain of the  $\alpha 3$  chain of collagen type IV. Sometimes the anti-GBM antibodies cross-react with antigens in the lung alveoli, resulting in simultaneous lung and kidney lesions (*Goodpasture syndrome*). It is clear that anti-GBM antibody GN is an autoimmune disease, so any one of the several mechanisms discussed earlier in relation to autoimmunity (*Chapter 13*) can be used to explain the disease.

Although anti-GBM antibody GN accounts for less than 1% of human GN cases, the resulting disease is as severe as the cause of renal injury in Goodpasture syndrome (*Chapter 13*). Many instances of anti-GBM antibody GN result in severe glomerular damage with crescents and the development of the clinical syndrome of rapidly progressive glomerulonephritis in the diagnosis of glomerular disease.

Antibodies may also react in situ with previously "planted" nonglomerular antigens, which may localize in various intrinsic components of the glomerulus. Planted antigens include DNA, which has an affinity for antibodies; products, such as endostreptosin, a protein of group A streptococci; large aggregated proteins (e.g., fibrin) in the mesangium because of their size; and immune complexes themselves, because they continue to react with free antibody, free antigen, or complement. Most of these planted antigens induce a granular pattern of immune complex deposition seen by immunofluorescence microscopy.

Several factors affect glomerular localization of antigen, antibody, or complexes. The molecular weight of the antigen, antibody, or complex is clearly important. The pattern of localization is also affected by changes in glomerular hemodynamics and the charge-selective barrier in the glomerulus. The localization of antigen, antibody, or immune complex deposition in the glomerular injury response. Studies in experimental models have shown that complexes deposited on the endothelium or subendothelium elicit an inflammatory reaction in the glomerulus with infiltration of inflammatory cells. Complexes directed to distal zones of the GBM (epithelium and subepithelium) are largely noninflammatory and are characteristic of Heymann nephritis or membranous nephropathy.

To conclude the discussion of antibody-mediated injury, it should be clear that *antibody deposition in the glomerulus leads to glomerular injury* and that immune reactions in situ, trapping of circulating complexes, interactions with glomerular structures, hemodynamic and structural determinants in the glomerulus all contribute to the morphologic and clinical features of the disease.

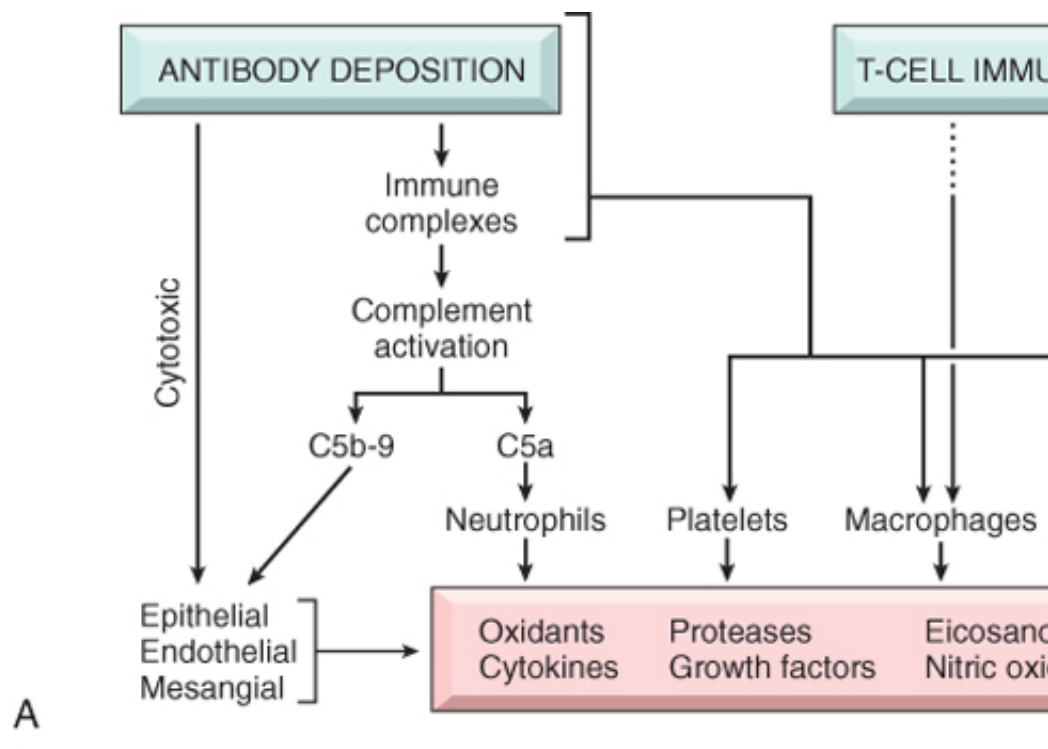
### **Cell-Mediated Immune Glomerulonephritis**

It has often been suggested that sensitized T cells, formed during the course of a cell-mediated injury. In some forms of experimental GN in rodents, the disease can be induced by transfer of sensitized T cells. This may account for the instances of GN in which either there are no deposits of antibodies or immune complexes. The degree of damage may correlate with the severity of damage. Even when antibodies are present, T-cell-mediated injury can be significant. Despite these intriguing hypotheses, it has been difficult to establish a causal role of T cells or cell-mediated injury in humans.

### Mediators of Immune Injury

Glomerular damage, reflected by loss of glomerular barrier function, is manifested by proteinuria and a fall in GFR. Once immune reactants are localized in the glomerulus, how does glomerular damage ensue? In some forms of GN, injury is complement-leukocyte-mediated (Fig. 14-5A). Activation of complement leads to the generation of C5a and the recruitment of neutrophils and monocytes. Neutrophils release proteases, which cause cell damage; and arachidonic acid metabolites, which contribute to redox injury. This model applies only to some types of GN, because many types show few neutrophils in the damaged glomerulus. In complement-dependent but not neutrophil-dependent injury, due to an effect of the C5-C9 lytic complex, which causes epithelial cell detachment and stimulates mesangial and epithelial cell injury. The membrane attack complex also up-regulates transforming growth factor- $\beta$  (TGF- $\beta$ ) receptor expression and synthesis of extracellular matrix, thus giving rise to altered GBM composition and thickening.

Antibodies directed to glomerular cell antigens may also be directly cytotoxic to glomerular cells. Such damage occurs in those disorders in which immune complexes are not found. Other mediators of glomerular injury include: (1) *macrophages*, which infiltrate the glomerulus in antibody- and cell-mediated reactions and, when activated, release biologically active molecules; (2) *platelets*, which aggregate in the glomerulus during immune-mediated injury and release growth factors; (3) *resident glomerular cells* (epithelial, mesangial, and endothelial), which can be directly injured by cytotoxic antibodies and release cytokines (interleukin 1), arachidonic acid metabolites, growth factors, *nitric oxide*, and endothelin. These mediators, which cause leukocyte infiltration and glomerular cell proliferation as a consequence of intraglomerular injury, are the mediators described in our discussion of inflammation in Chapter 2 may contribute to glomerular injury.







Antibody-mediated immune injury is an important mechanism of glomerular complement- and leukocyte-mediated pathways. Antibodies may also be directed against the glomerulus. The most common forms of antibody-mediated GN are caused by circulating immune complexes, which may involve exogenous (e.g. microbial antigens (e.g. in SLE). Immune complexes show a granular pattern of deposition against components of the GBM are the cause of anti-GBM-mediated disease, a severe injury. The pattern of antibody deposition is linear. Antibodies may also be directed against antigens that are planted in the GBM. The resultant in situ immune complex shows a pattern of deposition.

We now turn to a consideration of specific types of GN and the glomerular syndromes they produce.

### The Nephrotic Syndrome

The nephrotic syndrome refers to a clinical complex that includes the following: (1) massive proteinuria of 3.5 gm or more in adults; (2) hypoalbuminemia, with plasma albumin levels less than 3 gm/dL; (3) clinical manifestation; and (4) hyperlipidemia and lipiduria. At the onset there is little or no azotemia.

The components of the nephrotic syndrome bear a logical relationship to one another. The initial event is damage to the walls of the glomeruli, resulting in increased permeability to plasma proteins. It will be remembered that in the normal kidney that the glomerular capillary wall, with its endothelium, GBM, and podocytes, acts as a barrier that the filtrate must pass. Any increased permeability resulting from either structural or physicochemical changes allows the plasma into the glomerular filtrate. With long-standing or extremely heavy proteinuria, serum albumin levels fall, resulting in hypoalbuminemia. The generalized edema of the nephrotic syndrome is, in turn, a consequence of decreased oncotic pressure as a result of hypoalbuminemia, and primary retention of salt and water by the kidney. As a result, the tissues, there is a concomitant drop in plasma volume, with diminished glomerular filtration. Combined with the reduced GFR and reduction of secretion of natriuretic peptides, promotes retention of water, further aggravating the edema. By repetition of this chain of events, generalized edema (termed as the nephrotic syndrome) is more obscure. Presumably, hypoalbuminemia triggers increased synthesis of lipoproteins and abnormal transport of circulating lipid particles and impairment of peripheral breakdown of lipoproteins, resulting in increased permeability of the GBM to lipoproteins.

The relative frequencies of the several causes of the nephrotic syndrome vary according to age. In the young, for example, the nephrotic syndrome is almost always caused by a lesion primary to the kidney, such as minimal-change disease, focal segmental glomerulosclerosis, and membranoproliferative GN. In older age, for example, the nephrotic syndrome is almost always caused by a lesion secondary to the kidney, such as renal manifestations of a systemic disease. The most frequent systemic causes of the nephrotic syndrome are diabetes mellitus, amyloidosis, and SLE. The renal lesions produced by these disorders are described in [Chapter 5](#). The glomerular lesions that characteristically lead to the nephrotic syndrome are focal and segmental glomerulosclerosis (FSGS) and membranoproliferative GN (MPGN). The latter is more important in children; the former in adults. Two other primary glomerular diseases, IgA nephropathy and membranoproliferative GN, also produce the nephrotic syndrome. These four lesions are discussed in [Chapter 5](#).

**Table 14-2. Causes of Nephrotic Syndrome**

<b>Cause</b>
<b>Primary Glomerular Disease</b>
Membranous GN
Minimal-change disease
Focal segmental glomerulosclerosis
Membranoproliferative GN
IgA nephropathy and others
<b>Systemic Diseases with Renal Manifestations</b>
Diabetes mellitus†
Amyloidosis†

Systemic lupus erythematosus
Ingestion of drugs (gold, penicillamine <sup>®</sup> , "street heroin")
Infections (malaria, syphilis, hepatitis B, HIV)
Malignancy (carcinoma, melanoma)
Miscellaneous (bee-sting allergy, hereditary nephritis)

\*Approximate prevalence of primary disease is 95% of the cases in children, 60% in adults. Approximate prevalence of systemic disease in adults.  
GN, glomerulonephritis; HIV, human immunodeficiency virus.

### ***Minimal-Change Disease (Lipoid Nephrosis)***

This relatively benign disorder is the most frequent cause of the nephrotic syndrome in children. It has a normal appearance by light microscopy but shows diffuse effacement of podocyte foot processes on electron microscopy. Although it may develop at any age, this condition is most common between ages 1 and 5 years.

#### ***Pathogenesis***

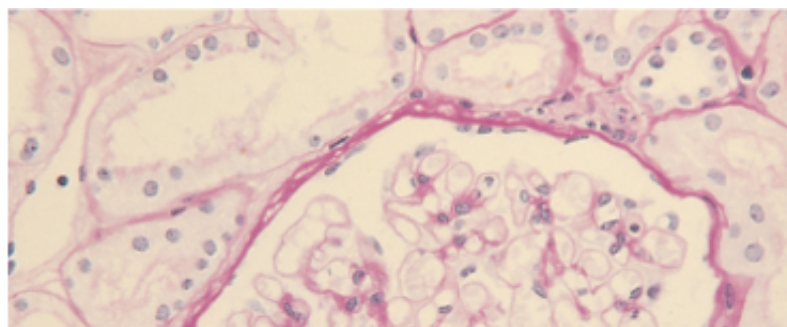
The pathogenesis of proteinuria in minimal change disease remains to be clearly elucidated. Basal proteinuria has been attributed to a T-cell derived factor that causes podocyte damage and effacement; the nature of such a putative factor nor a causal role of T cells is established in the human disease model of minimal change disease.

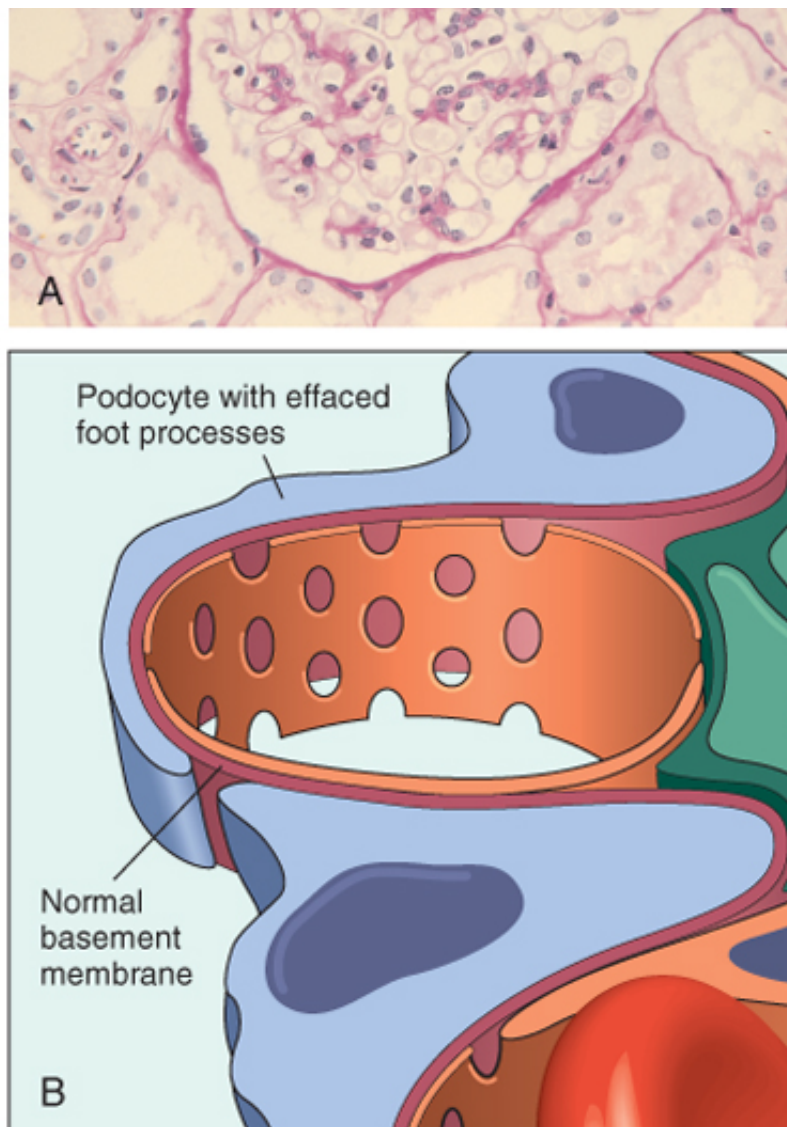
#### **Morphology**

With the light microscope, the glomeruli in minimal change disease appear normal; the proximal convoluted tubules are often heavily laden with protein droplets and lipid. The loss of protein to tubular reabsorption of the lipoproteins passing through the diseased glomeruli. The proximal convoluted tubules is the basis for the older term for this disorder, **lipoid nephrosis**. On electron microscopy, the GBM appears normal. The only obvious glomerular abnormality is the **diffuse effacement of the foot processes of the podocytes** (Fig. 14-6B). The cytoplasm of the podocytes thus appears flattened over the external aspect of the GBM, obliterating the network of foot processes. There are also epithelial cell vacuolization, microvillus loss, and focal detachments. When the changes in the podocytes reverse (e.g., in response to corticosteroid therapy), proteinuria remits.

#### ***Clinical Course***

The disease manifests itself by the insidious development of the nephrotic syndrome in an otherwise healthy child. Hypertension, and renal function is preserved in most individuals. The protein loss is usually confined to albumin (selective proteinuria). The prognosis in children with this disorder is good. More than 90% respond to corticosteroid therapy; however, proteinuria recurs in more than two-thirds of the initial responders. Less than 5% develop chronic renal failure after 25 years, and it is likely that most persistent proteinuria is caused by focal and segmental glomerulosclerosis not detected by biopsy. Because minimal change disease must be differentiated from other causes of the nephrotic syndrome in children, as other diseases also respond to steroid therapy, but the response is slower and relapses are more common.





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 Figure 14-6 Minimal change disease. **A**, Under the light microscope the PAS-stained glomerulus appears nor  
 Schematic diagram illustrating diffuse effacement of foot processes of podocytes with i

### ***Focal and Segmental Glomerulosclerosis***

Focal segmental glomerulosclerosis (FSGS) is a lesion characterized histologically by sclerosis at involvement) and involving only segments of each affected glomerulus. This histologic picture is o syndrome and can occur (1) in association with other known conditions, such as human immunod (human immunodeficiency virus nephropathy, heroin nephropathy); (2) as a secondary event in o [IgA] nephropathy); (3) as a maladaptation after nephron loss (described above); (4) in inherited o mutations affecting cytoskeletal or related proteins expressed in podocytes (e.g., nephrin); or (5) a

Primary (or idiopathic) FSGS accounts for approximately 20% to 30% of all cases of the nephrotic common cause of nephrotic syndrome in adults and remains a frequent cause in children. *In child cause of the nephrotic syndrome from MCD*, because the clinical courses are markedly different. of hematuria and hypertension in persons with this lesion; their proteinuria is nonselective, and in therapy is poor. At least 50% of individuals with FSGS develop end-stage renal failure within 10 y, even less well than children.



### Pathogenesis

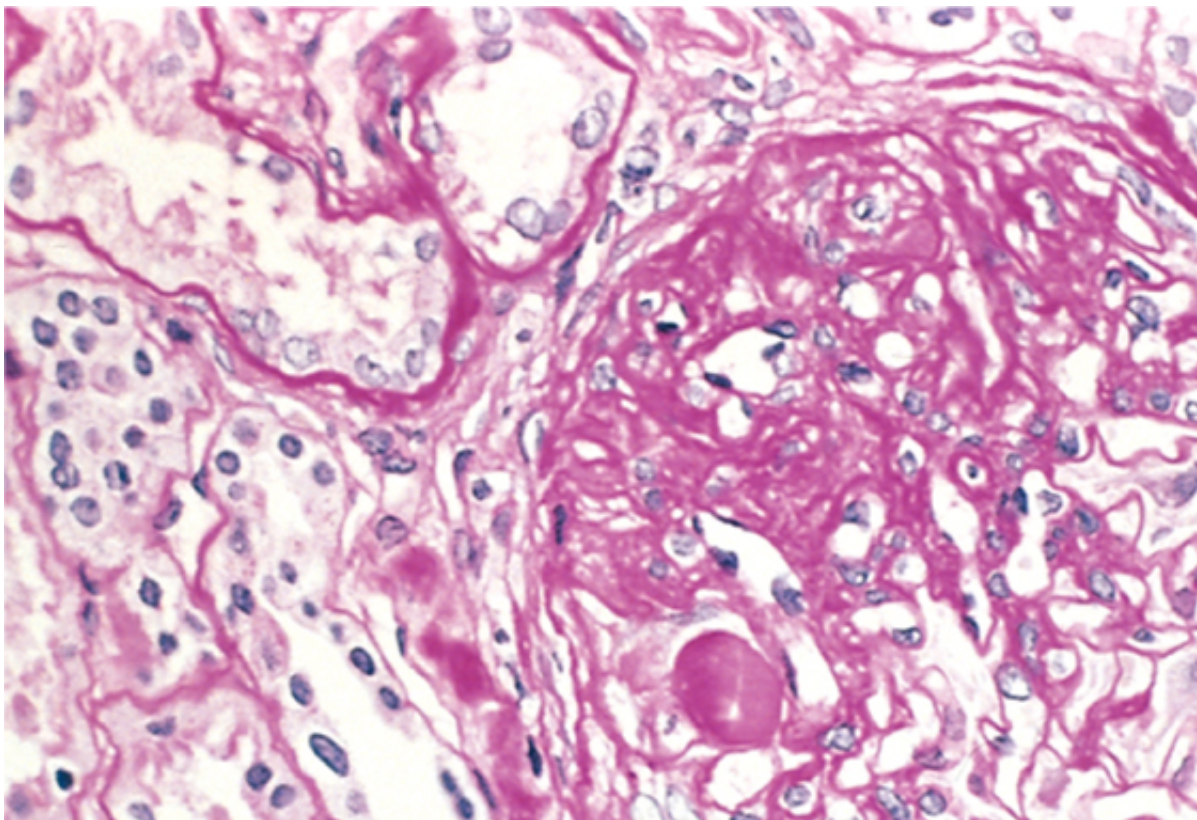
The pathogenesis of primary FSGS is unknown. Some investigators have suggested that FSGS and MCD may transform into FSGS. Others believe them to be distinct clinicopathologic entities from 1 *podocytes is thought to represent the initiating event of primary FSGS*. As with MCD, permeability lymphocytes have been proposed. The deposition of hyaline masses in the glomeruli represents the lipids in foci of injury where sclerosis develops. IgM and complement proteins commonly seen in the nonspecific entrapment in damaged glomeruli. The recurrence of proteinuria in some persons with sometimes within 24 hours of transplantation, supports the idea that a circulating mediator is the cause.

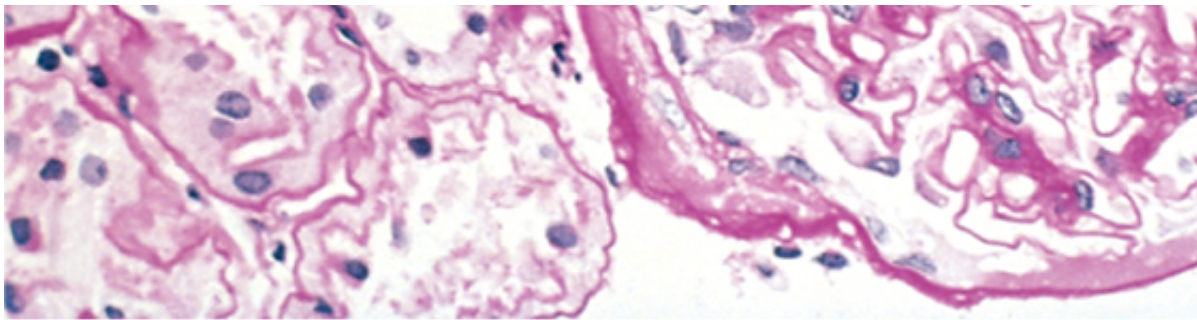
### Morphology

In FSGS, the disease first affects only some of the glomeruli (hence the term "**focal**" juxtamedullary glomeruli. With progression, eventually all levels of the cortex are affected. FSGS is characterized by lesions occurring in some tufts within a glomerulus and segments (hence the term "**segmental**"). Thus, the involvement is both focal and segmental. Affected glomeruli exhibit **increased mesangial matrix, obliterated capillary lumens, and hyaline masses (hyalinosis) and lipid droplets**. Occasionally, glomeruli are completely sclerosed. In affected glomeruli, immunofluorescence microscopy often reveals no immunoglobulins, usually IgM, and complement in the areas of hyalinosis. On electron microscopy, podocytes exhibit **effacement of foot processes**, as in MCD.

In time, progression of the disease leads to global sclerosis of the glomeruli with proteinuria and interstitial fibrosis. This advanced picture is difficult to differentiate from other focal glomerular diseases, described below.

A morphologic variant called **collapsing glomerulopathy** is being increasingly reported. It is characterized by collapse of the entire glomerular tuft and podocyte hyperplasia. This is a more severe form of FSGS that may be idiopathic or associated with human immunodeficiency virus infection and certain drugs. It carries a particularly poor prognosis.





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Figure 14-7 High-power view of focal and segmental glomerulosclerosis (PAS stain), seen as a mass of scarred, eosinophilic matrix material, that has replaced a portion of the glomerulus. (Courtesy of Dr. H. Rennke, Department of Pathology, Harvard Medical School, Boston, Massachusetts.)

### Clinical Course

There is little tendency for spontaneous remission of idiopathic FSGS, and responses to corticosteroids are variable. Progression to renal failure occurs at varying rates, and about 50% of individuals suffer renal failure within 10 years.

### Membranous Nephropathy (Membranous Glomerulonephritis)

This slowly progressive disease, most common between 30 and 50 years of age, is characterized by *subepithelial immunoglobulin-containing deposits along the GBM*. Early in the disease, the glomerular architecture is preserved, but well-developed cases show *diffuse thickening of the capillary wall*.

Membranous nephropathy is idiopathic in about 85% of cases. In the remainder (secondary membranous nephropathy), it is secondary to other disorders, including: (1) infections (chronic hepatitis B, syphilis, schistosomiasis); (2) malignancies (particularly carcinoma of the lung and colon and melanoma); (3) SLE and other autoimmune conditions; (4) drugs (gold, mercury); and (5) drugs (penicillamine<sup>®</sup>, captopril<sup>®</sup>, nonsteroidal anti-inflammatory agents).

### Pathogenesis

Membranous GN is a form of chronic immune complex nephritis. Although circulating complexes (antibody-antigen complexes) or endogenous (DNA in SLE) antigen can cause membranous nephropathy, it is now thought to be caused by antibodies reacting in situ to endogenous or planted glomerular antigens.

The experimental model of membranous GN is Heymann nephritis, which is induced in animals by antibodies to glomerular basement membrane (GBM) proteins. The antibodies that are produced react with an antigen located in the GBM, resulting in "immune complex formation" and proteinuria without severe inflammation. Idiopathic membranous nephropathy is an autoimmune disease caused by antibodies to a renal autoantigen that remains unidentified.

In the presence of immune deposits, how does the glomerular capillary wall become leaky? In the presence of immune deposits and in the virtually uniform presence of complement, current work points to a direct action of complement, on the podocyte. The membrane attack complex causes activation of glomerular cells, inducing them to liberate proteases and oxidants that can damage capillary walls, with consequent proteinuria.

### Morphology

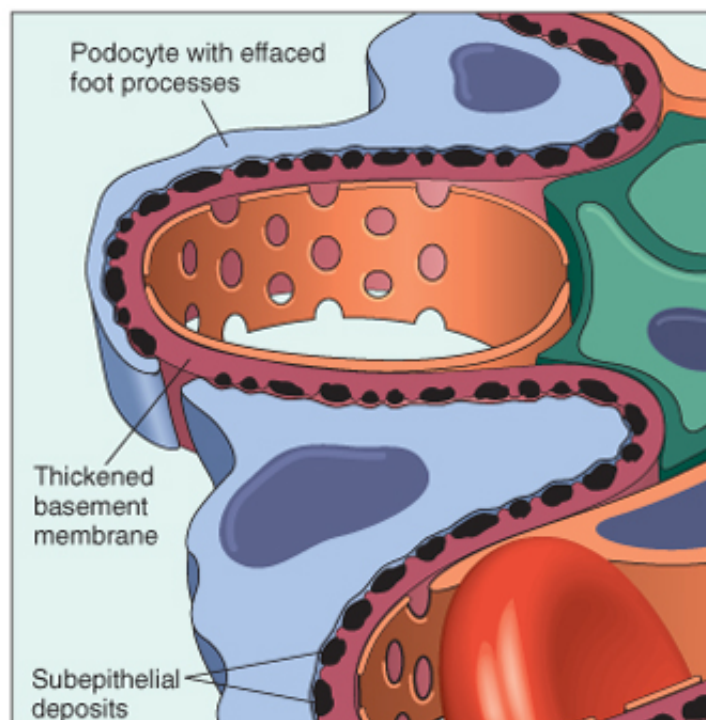
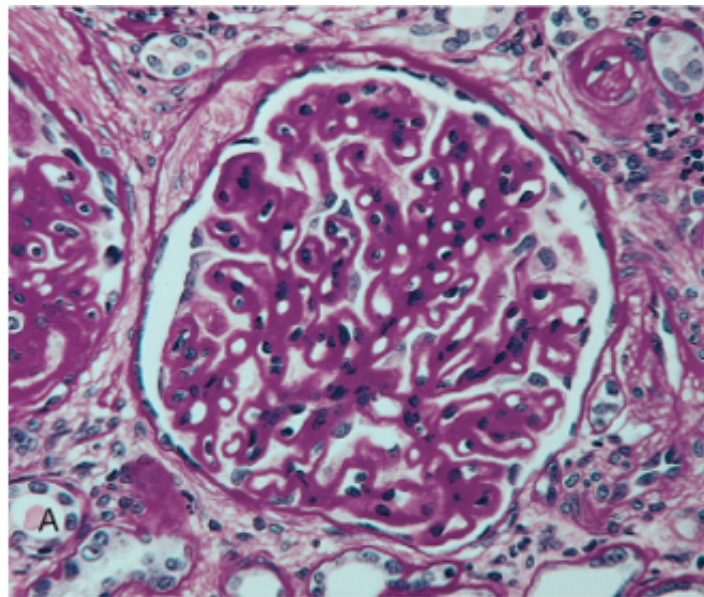
Seen by light microscopy with H&E stain, the basic change in membranous nephropathy is **diffuse thickening of the GBM** (Fig. 14-8A). By electron microscopy, this appears to be caused in part by **subepithelial deposits** that nestle against the GBM and in part by small, spikelike protrusions of GBM matrix that form in reaction to the deposits (**spike pattern**) (Fig. 14-8B). As the disease progresses, these spikes close over the deposits. In addition, the podocytes show **effacement of foot processes**. Later in the disease, incorporated deposits may be catabolized and eventually disappear, leaving cavities. Continued deposition of basement membrane matrix leads to progressively thicker GBM. With further progression, the glomeruli can become sclerosed. Immunofluorescence

typical **granular deposits** of immunoglobulins and complement along the GBM (see

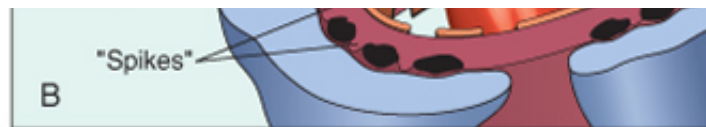
### *Clinical Course*

The onset in idiopathic cases is characterized by the insidious development of the nephrotic syndrome. However, some individuals with membranous nephropathy may have lesser degrees of proteinuria and edema. In contrast to minimal change disease, the proteinuria is nonselective, with urinary loss of high molecular weight proteins, and does not usually respond to corticosteroid therapy. Secondary causes of membranous nephropathy include drugs, infections, and systemic diseases. Membranous nephropathy follows a notoriously variable and often indolent course. Overall, although most individuals with membranous nephropathy progress to end-stage renal disease, about 40% suffer progressive disease terminating in renal failure. An additional 10% to 30% have a more benign course with partial or complete remission of proteinuria.

### **Membranoproliferative Glomerulonephritis**



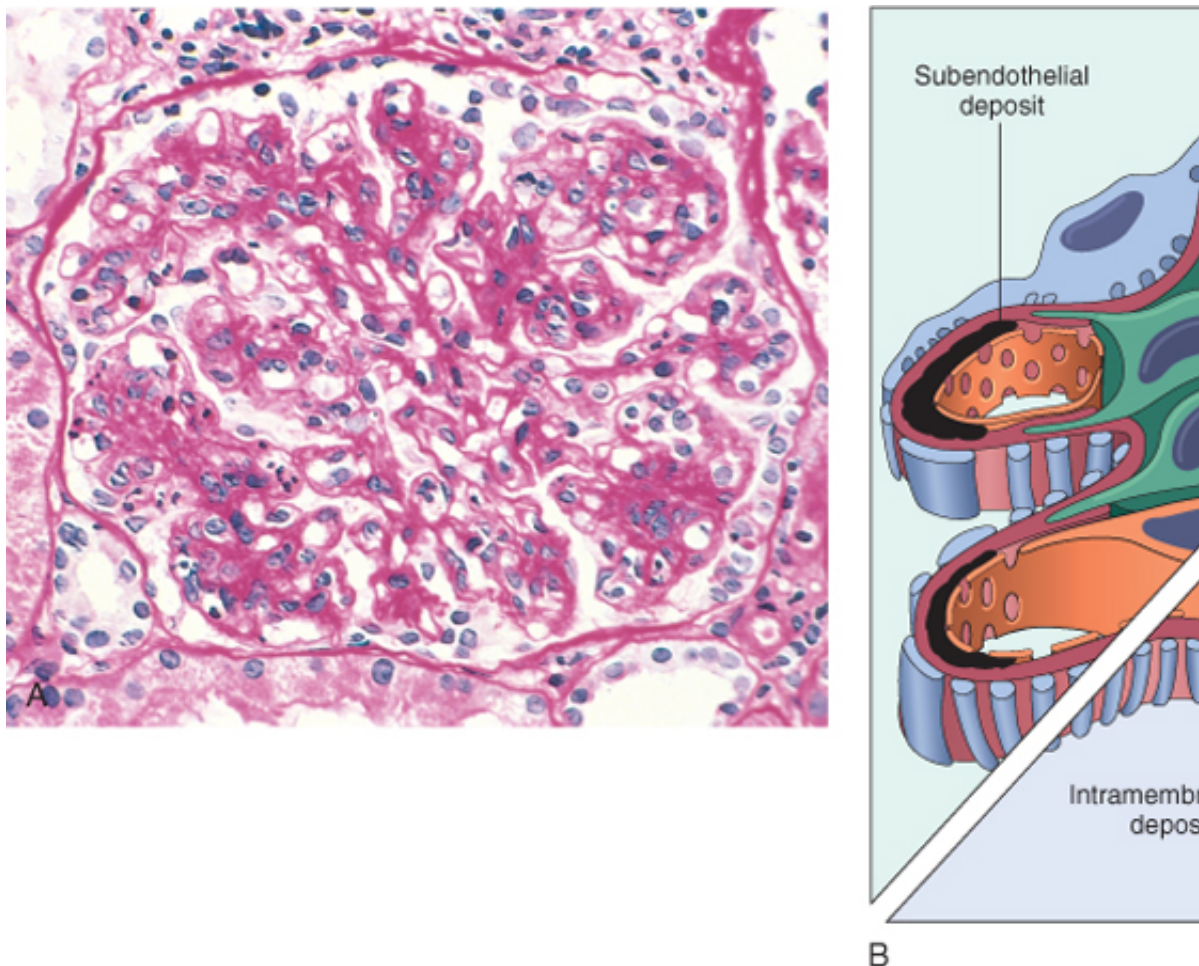




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Figure 14-8 Membranous nephropathy. **A**, Diffuse thickening of the glomerular basement membrane. **B**, Schematic representation of effacement of foot processes, and the presence of "spikes" of basement membrane material between the podocytes.

Membranoproliferative GN (MPGN) is manifested histologically by alterations in the GBM and mesangial cells. It accounts for 5% to 10% of cases of idiopathic nephrotic syndrome in children and adults. It is characterized by hematuria or proteinuria in the non-nephrotic range; others have a combined nephrotic-nephritic picture. Type I and II are recognized on the basis of distinct ultrastructural, immunofluorescence microscopic, and clinical features. Type I is far more common (about 80% of cases).

### Pathogenesis



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Figure 14-9 **A**, Membranoproliferative GN, showing mesangial cell proliferation, basement membrane thickening, and a lobular architecture. **B**, Schematic representation of patterns in the two types of membranoproliferative GN. In type I (dense-deposit disease), subendothelial deposits (orange) and intramembranous deposits (green) are present. In type II (dense-intramembranous disease), intramembranous deposits (green) and subendothelial deposits (orange) are present. In both, mesangial interposition gives the characteristic lobular appearance when viewed by light microscopy.

Different pathogenic mechanisms are involved in the development of type I and type II disease. Type I is caused by circulating immune complexes, akin to chronic serum sickness, but the inciting antigen is not known. Type II is caused by a monoclonal immunoglobulin depositing in the glomerulus.



in association with hepatitis B and C antigenemia, SLE, infected atrioventricular shunts, and extra-episodic antigenemia. The pathogenesis of type II MPGN, also known as *dense-deposit disease*, *abnormality appears to be excessive complement activation*, which may be caused by several mechanisms. Some patients have an autoantibody against C3 convertase, called *C3 nephritic factor*, which is believed to cause uncontrolled cleavage of C3 and activation of the alternative complement pathway. Mutations in the regulatory protein *Factor H* have been described in some patients. These mutations may lead to a defective function of the protein, again resulting in excessive complement activation. Functional impairment may also be caused by autoantibodies, or abnormalities in the C3 protein that prevent its interaction with Factor H. In type II, the glomerular changes are produced in part by excessive consumption of C3 and in part by reduced synthesis of C3. Complement abnormality induces the glomerular changes. Because of these important differences in pathogenesis and ultrastructural appearance, there is a growing trend to separate this diagnostic category and consider it distinct from MPGN type I.

### Morphology

By light microscopy, both types of MPGN are similar. The glomeruli are large, with increased cellularity, and show **proliferation of mesangial and endothelial cells** as well as hypercellularity (Fig. 14-9A). The **GBM is thickened**, and the glomerular capillary wall often shows "tram track," appearance, especially evident in silver or periodic acid-Schiff (PAS) stain. There is **"splitting" of the GBM** due to the inclusion within it of processes of mesangial and endothelial cells extending into the peripheral capillary loops (Fig. 14-9B).

Types I and II have different ultrastructural and immunofluorescence microscopic features. **Type I MPGN** is characterized by discrete **subendothelial electron-dense deposits**. By immunofluorescence microscopy, C3 is deposited in an irregular granular pattern, and complement components (C1q and C4) are often also present, indicative of an immune-mediated pathogenesis.

In **type II lesions** the lamina densa and the subendothelial space of the GBM are filled with an irregular, ribbon-like, extremely electron-dense structure, resulting from the dense deposit composition, giving rise to the term **dense-deposit disease**. C3 is present in irregular linear foci in the basement membranes and in the mesangium in characteristic circular (mesangial rings). IgG is usually absent, as are the early components of the classical pathway (C1q and C4).

### Clinical Course

The principal mode of presentation (in ~50% of cases) is the nephrotic syndrome, although MPGN may also present with hematuria and proteinuria. The prognosis of MPGN is generally poor. In one study, none of 60 patients followed into remission. Forty percent progressed to end-stage renal failure, 30% had variable degrees of renal impairment, and 30% had persistent nephrotic syndrome without renal failure. Dense-deposit disease has a worse prognosis than type I MPGN. Like many other GNs, MPGN, usually type I, may occur in association with other diseases (secondary MPGN), such as SLE, hepatitis B and C, chronic liver disease, and chronic bacterial infections. In type II, the disease is believed to be associated with hepatitis C and related cryoglobulinemia.

### SUMMARY

#### The Nephrotic Syndrome

The nephrotic syndrome is characterized by proteinuria, which results in hypoproteinemia and edema. Podocyte injury is an underlying mechanism of proteinuria, and may be caused by nonimmune causes (as in MCD and FSGS) or immune mechanisms (as in IgA nephropathy). *Minimal change disease (MCD)* is the most frequent cause of nephrotic syndrome in children. It is characterized by proteinuria and effacement of glomerular foot processes without antibody deposits. The disease responds well to steroid therapy. *Focal and segmental glomerulosclerosis (FSGS)* may be primary (podocyte injury by unknown mechanisms) or secondary as a consequence of prior glomerulonephritis, hypertension or infection such as

obliteration of capillary lumens, hyaline deposits and loss of foot processes; resistant to therapy and may progress to end stage renal disease. *Membran* caused by an autoimmune response against an unknown renal antigen; it is subepithelial deposits of antibodies with GBM thickening and loss of foot process inflammation; the disease is often resistant to steroid therapy.

## The Nephritic Syndrome

The nephritic syndrome is a clinical complex, usually of acute onset, characterized by (1) *hematuria*, blood cell casts in the urine, (2) some degree of *oliguria* and azotemia, and (3) *hypertension*. Although and even edema, these are usually not as severe as in the nephrotic syndrome. The lesions that are common proliferation of the cells within the glomeruli, accompanied by a leukocytic infiltrate. This thickens the walls, permitting escape of red cells into the urine, and induces hemodynamic changes that lead to a fall in GFR is manifested clinically by oliguria, reciprocal fluid retention, and azotemia. Hypertension is present and some augmented renin release from the ischemic kidneys.

The acute nephritic syndrome may be produced by systemic disorders such as SLE, or it may be produced by a localized process. The latter is exemplified by acute postinfectious GN.

### **Acute Postinfectious (Poststreptococcal) Glomerulonephritis**

Acute postinfectious GN, one of the more frequently occurring glomerular disorders, is typically characterized by immune complexes resulting in diffuse proliferation and swelling of resident glomerular cells and frequent infiltration by neutrophils. The inciting antigen may be exogenous or endogenous. The prototypic exogenous pathogen is *Streptococcus*. A similar proliferative GN may occur with other exogenous or endogenous antigens. Infections by organisms other than *Streptococcus* may also be associated with diffuse postinfectious GN. These include certain pneumococcal and staphylococcal infections. Common viral diseases such as mumps, measles, chickenpox, and hepatitis B and C. Endogenous antigens may cause a proliferative GN, but more commonly in a membranous nephropathy pattern (see above), which is characteristic of postinfectious GN.

The classic case of poststreptococcal GN develops in a child 1 to 4 weeks after the individual recovers from a recent infection. Only certain "nephritogenic" strains of  $\beta$ -hemolytic streptococci are capable of evoking glomerulonephritis. The initial infection is localized to the pharynx or skin.

### *Pathogenesis*

It is generally agreed that immune complex deposition is involved in the pathogenesis of acute postinfectious GN. In immune complex disease, such as hypocomplementemia and granular deposits of IgG and complement. The relevant antigens are probably streptococcal proteins, but their identity is not established. It is also formed mainly in the circulation or in situ (the latter by binding of antibodies to bacterial antigens) so that C3 may be deposited on the GBM before IgG; hence, the primary injury might be by complement complexes are formed.

### **Morphology**

By light microscopy, the most characteristic change in postinfectious GN is a fairly marked **cellularity** of the glomerular tufts that affects nearly all glomeruli, hence the term "hypercellular". Increased cellularity is caused both by proliferation and swelling of endothelial and mesangial cells and by a neutrophilic and monocytic infiltrate. Sometimes there is necrosis of the capillary walls. There may also be "crescents" (described next) within the urinary space in response to the injury. In general, these findings are ominous. Electron microscopy shows deposits arrayed as subendothelial, intramembranous, or, most often, **subepithelial "humps"** on the GBM (Fig. 14-10B). Mesangial deposits are also occasionally present. Immunofluorescence shows scattered **granular deposits of IgG and complement** within the capillary walls corresponding to the deposits visualized by electron microscopy. These deposits are usually present for a period of about 2 months.

### *Clinical Course*

The onset of the kidney disease tends to be abrupt, heralded by malaise, a slight fever, nausea, and vomiting. In some cases, oliguria, azotemia, and hypertension are only mild to moderate. Characteristically, the urine is smoky brown rather than bright red. Some proteinuria is a constant feature of the disease, and as severe enough to produce the nephrotic syndrome. Serum complement levels are low during the acute phase. Anti-streptolysin O antibody titers are elevated in poststreptococcal cases.

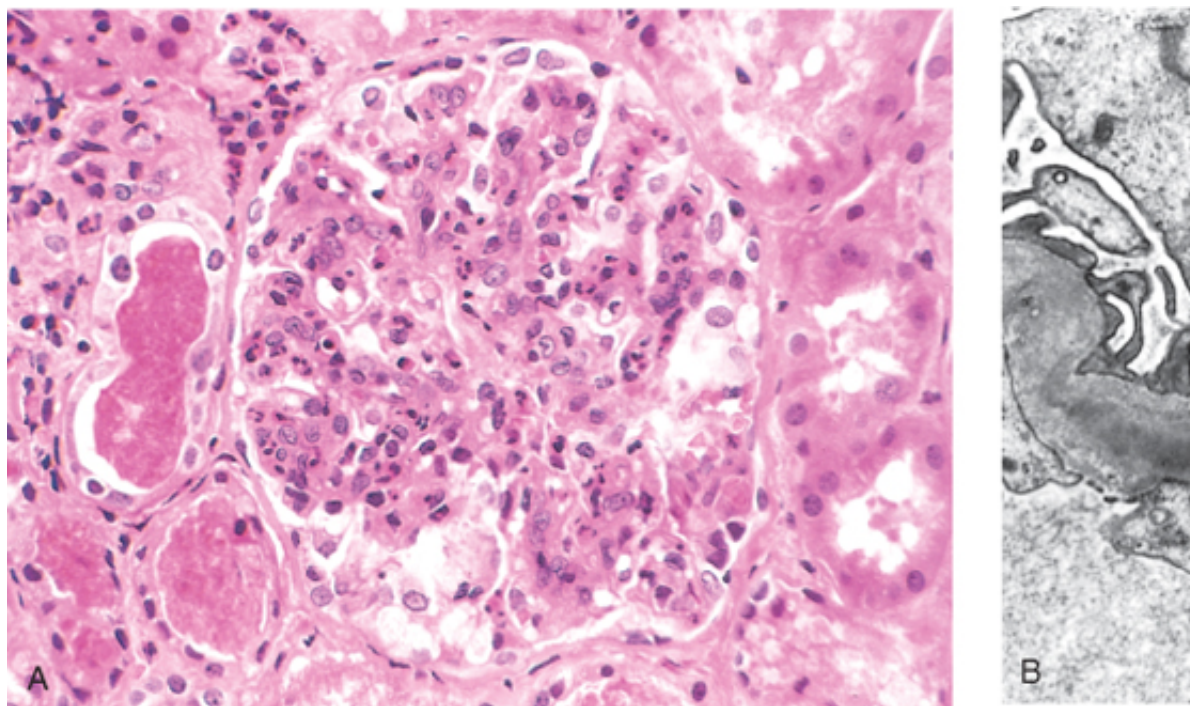
Recovery occurs in most children in epidemic cases. Some children develop rapidly progressive (FSGS) chronic renal disease due to secondary scarring. The prognosis in sporadic cases is less clear. In adults, they develop end-stage renal disease over the ensuing few years or 1 to 2 decades, depending on the severity. In contrast, in children, the prevalence of chronicity after sporadic cases of acute postinfectious GN is low.

### ***IgA Nephropathy (Berger Disease)***

This condition usually affects children and young adults and begins as an episode of gross hematuria following a nonspecific upper respiratory tract infection. Typically, the hematuria lasts several days and then subsides. It is often associated with loin pain. *IgA nephropathy is one of the most common causes of recurrent gross hematuria and the most common glomerular disease revealed by renal biopsies worldwide.*

*The pathogenic hallmark is the deposition of IgA in the mesangium.* Some have considered IgA nephropathy as a variant of Henoch-Schönlein purpura, also characterized by IgA deposition in the mesangium. In contrast to Henoch-Schönlein purpura, which is a systemic syndrome involving the skin (purpuric rash), gastrointestinal tract (gastroenteritis), joints (arthritis), and kidneys.

### *Pathogenesis*



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Figure 14-10 Poststreptococcal GN. **A**, Glomerular hypercellularity is caused by intracapillary leukocytes and proliferating epithelial cell casts in the tubules. **B**, Typical electron-dense subepithelial "hump" (arrow) and intramembranous deposits. B, basement membrane; Ep, visceral epithelial cells (podocytes).

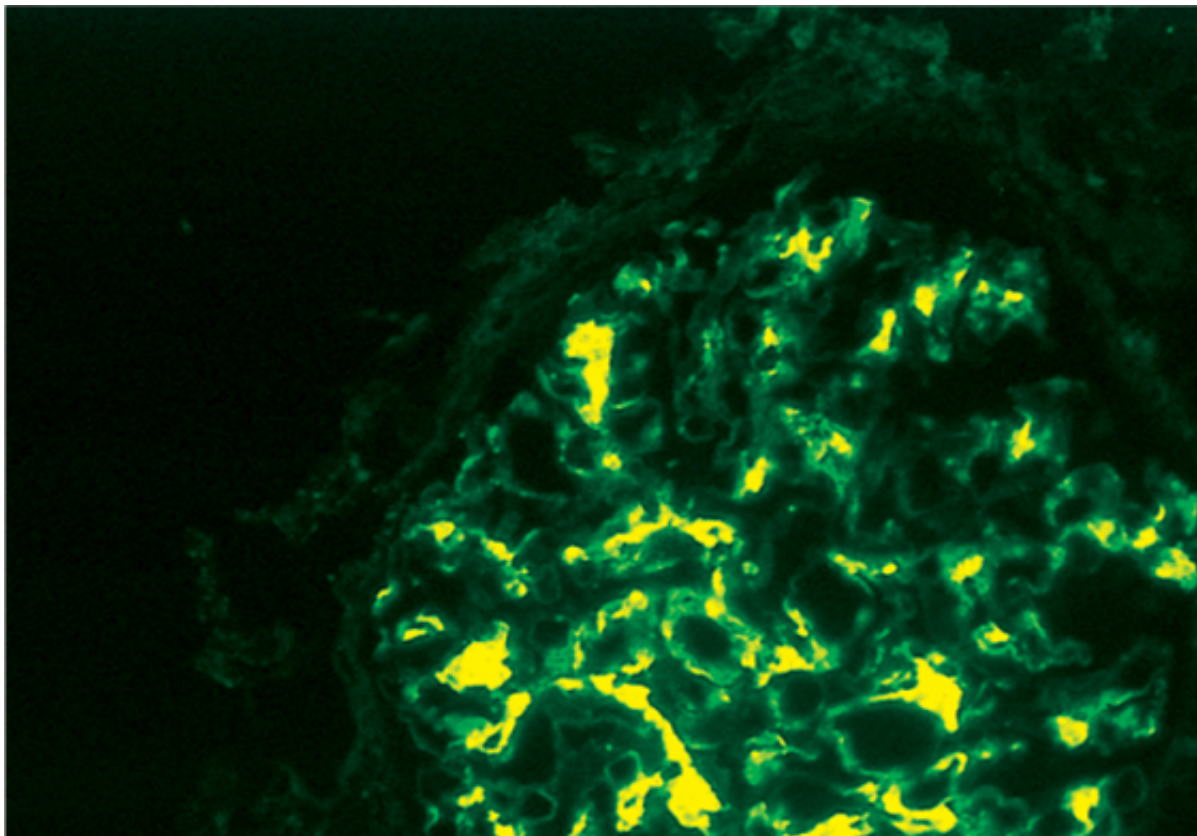
### **Morphology**



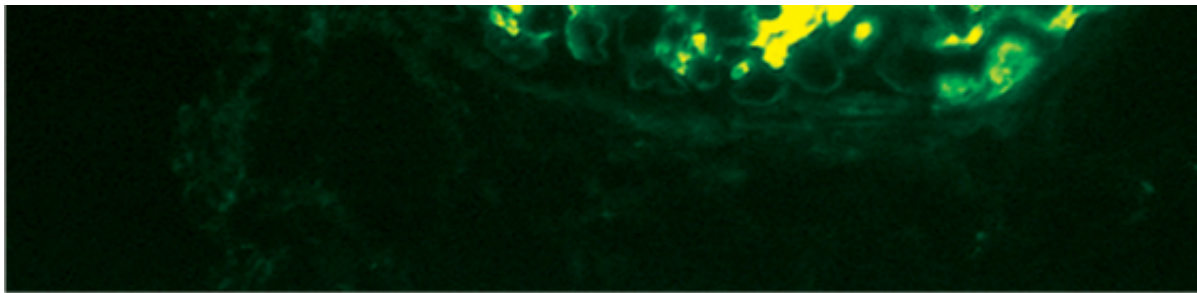
#### morphology

Histologically, the lesions in IgA nephropathy vary considerably. The glomeruli may show mesangial widening and segmental inflammation confined to some glomeruli (focal mesangial proliferation (mesangioproliferative); or (rarely) overt crescentic GN. The immunofluorescence picture is of **mesangial deposition of IgA**, often with C3 and small amounts of IgG or IgM (Fig. 14-11). Early components of the classical complement pathway are absent. Electron microscopy confirms the presence of electron-dense deposits in the mesangium; these deposits may extend to the subendothelial area of adjacent capillary walls in a minority of those with focal proliferation.

Accumulating evidence suggests that IgA nephropathy is associated with an abnormality in IgA production. IgA in mucosal secretions, is at low levels in normal serum but increased in 50% of patients. Increased production in the marrow. In addition, circulating IgA-containing immune complexes are present in some patients. Influence is suggested by the occurrence of this condition in families and in HLA-identical siblings. Certain HLA and complement phenotypes in some populations. Studies also suggest an abnormality in the clearance of IgA, a process that would reduce plasma clearance of IgA, thus favoring deposition in the mesangium. Mesangial deposition of IgA suggests entrapment of IgA immune complexes in the mesangium, a process that points to activation of the alternative complement pathway. Taken together, these clues suggest a response to respiratory or gastrointestinal exposure to environmental agents (e.g., viruses, bacteria). Deposition of IgA and IgA-containing immune complexes in the mesangium, where they activate the alternative complement pathway, leading to glomerular injury. In support of this scenario, IgA nephropathy occurs with increased frequency in patients with intestinal mucosal defects are seen, and in liver disease where there is defective hepatobiliary clearance (IgA nephropathy). **Clinical Course.** The disease most often affects children and young adults. More than 50% present with gross hematuria after an infection of the respiratory or, less commonly, gastrointestinal tract. Microscopic hematuria, with or without proteinuria; and 5% to 10% develop a typical acute nephritis. The acute course lasts for several days and then subsides, only to return every few months. The subsequent course is usually benign, with most patients maintaining normal renal function for decades. Slow progression to chronic renal failure occurs in 25% of patients.







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Figure 14-11 IgA nephropathy showing characteristic immunofluorescence deposition of IgA, pr

### **Hereditary Nephritis**

Hereditary nephritis refers to a group of hereditary glomerular diseases caused by mutations in *Glomerular basement membrane (GBM)*. *Alport syndrome*, in which nephritis is accompanied by nerve deafness and various eye disorders (cataracts, and corneal dystrophy).

#### **Pathogenesis**

The GBM is largely composed of type IV collagen, which is made up of heterotrimers of  $\alpha 3$ ,  $\alpha 4$ , and  $\alpha 5$ . Type IV collagen is crucial for normal function of the lens, cochlea, and glomerulus. Mutation of any one of these chains leads to a defective heterotrimer assembly, and thus the disease manifestations of Alport syndrome.

#### **Morphology**

Histologically, glomeruli in hereditary nephritis appear unremarkable until late in the course when glomerular sclerosis may occur. In some kidneys, interstitial cells take on a foamy appearance due to accumulation of neutral fats and mucopolysaccharides (**foam cells**) as a reaction to the disease. In late progression, there is increasing glomerulosclerosis, vascular sclerosis, tubular atrophy, and interstitial fibrosis. With the electron microscope, the basement membrane of glomeruli appears normal early in the course. Late in the course, the GBM develops irregular foci of thickening, prominent splitting and lamination of the lamina densa, yielding a "basket-weave" appearance.

#### **Clinical Course**

The inheritance is heterogeneous, being most commonly X-linked as a result of mutation of the gene for  $\alpha 5$  chain. Males therefore tend to be affected more frequently and more severely than females and are more likely to have progressive disease. Inheritance is autosomal recessive or dominant, linked to defects in the genes that encode  $\alpha 3$  or  $\alpha 4$  chains. Hereditary nephritis is present at age 5 to 20 years with gross or microscopic hematuria and proteinuria, usually beginning between 20 and 50 years of age.

Female carriers of X-linked Alport syndrome or carriers of either gender of the autosomal forms usually have mild disease, which is most often asymptomatic and follows a benign course.

In a few instances, a heterozygous defect in the  $\alpha 3$  or  $\alpha 4$  chains is associated with persistent, often microscopic hematuria (so-called benign familial hematuria, or thin basement membrane lesion).

### **SUMMARY**

#### **The Nephritic Syndrome**

The nephritic syndrome is characterized by hematuria, oliguria with azotemia, and hypertension. The most common causes are immunologically mediated glomerulonephritides, characterized by proliferative changes and leukocyte infiltration. *Acute post-glomerulonephritis* typically occurs after streptococcal infection in children and usually occurs following infection with many other organisms; it is caused by deposits of immune complexes mainly in the subendothelial spaces, with abundant neutrophils and proliferating epithelial cells.

Most affected children recover; the prognosis is worse in adults. *IgA nephropathy*, characterized by mesangial deposits of IgA-containing immune complexes, is the most common form of GN worldwide; it is also a common cause of recurrent hematuria; it occurs in children and young adults and has a variable course. *Hereditary nephritis* is caused by mutations in the gene encoding GBM collagen; it manifests as hematuria and slowly progressing renal function; glomeruli appear normal until late in the disease course.

### Rapidly Progressive (Crescentic) Glomerulonephritis

RPGN is a clinical syndrome and not a specific etiologic form of GN. Clinically, it is characterized by a rapid decline in renal function with features of the nephritic syndrome, often with severe oliguria and (if untreated) death within months. *Regardless of the cause, the histologic picture is characterized by the presence of crescentic glomeruli* in part by proliferation of the parietal epithelial cells of Bowman's capsule in response to injury and infiltration by macrophages.

#### Pathogenesis

Crescentic glomerulonephritis (CrGN) may be caused by a number of different diseases, some renal and some systemic. Although no single mechanism can explain all cases, there is little doubt that in most cases it is immunologically mediated. Thus, a practical classification divides CrGN into three groups on the basis of the underlying disease (Table 14-3). In each group, the disease may be associated with a known disorder or it may be idiopathic.

It will be obvious from the discussion below that although all three types of CrGN may be associated with a systemic disease, in some cases CrGN is idiopathic. When the cause can be identified, about 12% of individuals have type I CrGN (with or without lung involvement); 44% have type II CrGN; and the remaining 44% have severe glomerular injury.

#### Anti-Glomerular Basement Membrane Antibody (Type I) Crescentic Glomerulonephritis

*Anti-GBM antibody crescentic glomerulonephritis*, or type I CrGN, is characterized by linear deposits of anti-GBM antibody along the GBM, as described above. In some of these individuals the anti-GBM antibodies also bind to pulmonary basement membranes to produce the clinical picture of pulmonary hemorrhages associated with renal failure, known as *Goodpasture syndrome*, to distinguish their condition from so-called idiopathic cases in which renal failure occurs without pulmonary disease. Anti-GBM antibodies are present in the serum and are helpful in diagnosis. It is important to note that because these individuals benefit from plasmapheresis, which removes pathogenic antibodies from the circulation.

**Table 14-3. Crescentic Glomerulonephritis**

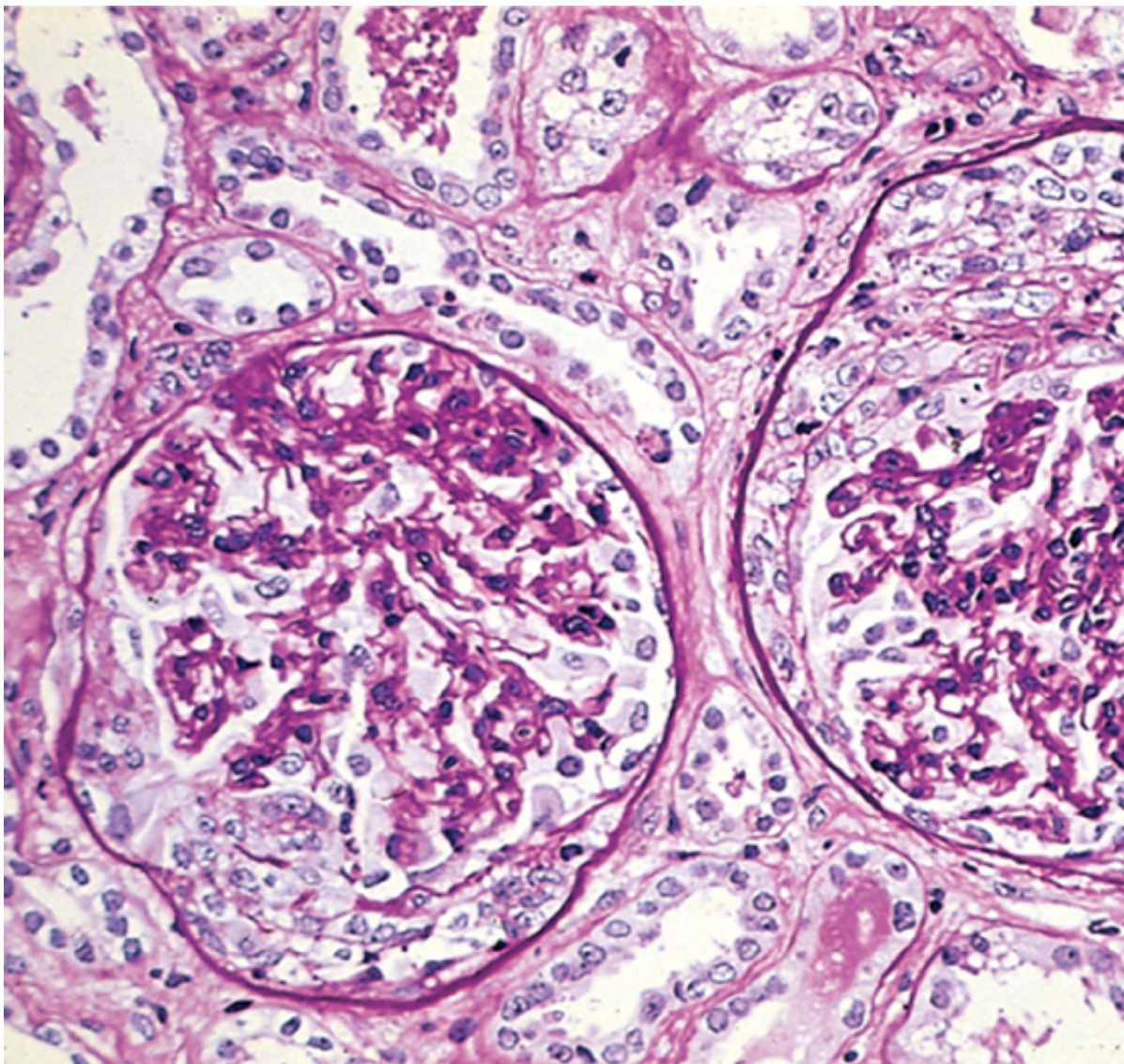
<b>Type I (Anti-GBM Antibody)</b>
Idiopathic
Goodpasture syndrome
<b>Type II (Immune Complex)</b>
Idiopathic
Postinfectious/infection related
Systemic lupus erythematosus
Henoch-Schönlein purpura/IgA nephropathy
<b>Type III (Pauci-Immune) ANCA Associated</b>
Idiopathic
Wegener granulomatosis
Microscopic angiitis

ANCA, antineutrophil cytoplasmic antibody; Anti-GBM, anti-glomerular basement membrane.

### Morphology

The kidneys are enlarged and pale, often with **petechial hemorrhages** on the cortex. They show segmental necrosis and GBM breaks, with resulting proliferation of the parietal cells in response to the exudation of plasma proteins including fibrin into Bowman's space. These proliferations are called **crescents** due to their shape as they fill Bowman's space both by proliferation of parietal cells and by migration of monocytes/macrophages (Figure 14-12). Smaller numbers of other types of leukocytes may also be present. The uninvolved glomerulus shows no proliferation. Immunofluorescence is characteristic with strongly deposited IgG and C3 along the GBM. However, deposits are not visualized by electron microscopy because the endogenous collagen IV antigen to which the antibody is reacting is deposited in the large lattices of antigens and antibodies that occur in deposited immune complexes. Electron microscopy may show distinct ruptures in the GBM. The crescents eventually fill Bowman's space and compress the glomeruli. Fibrin strands are prominent between the cellular crescent and the glomerular tuft. In time, crescents may undergo scarring.

### ***Immune Complex-Mediated (Type II) Crescentic Glomerulonephritis***



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 Figure 14-12 Crescentic GN (PAS stain). Note the collapsed glomerular tufts and the crescent-shaped mass of proliferating parietal cells and infiltrating leukocytes filling Bowman's space and compressing the glomerular tuft. ANCA, antineutrophil cytoplasmic antibody. (Courtesy of Dr. M. A. Venkatachalam, Department of Pathology, University of Texas Health Science Center, San Antonio, Texas.)



*Type II CrGNs are immune complex-mediated disorders.* This can be a complication of any of the poststreptococcal GN, SLE, IgA nephropathy, and Henoch-Schönlein purpura. In some cases, immune complex deposition is the underlying cause is undetermined. In all of these cases, immunofluorescence studies reveal a "lumpy-bumpy" pattern of staining of the GBM and/or mesangium for immunoglobulin and/or complement. Treatment is usually helped by plasmapheresis.

#### **Morphology**

There is severe injury with **segmental necrosis** and GBM breaks with resultant crescent formation as described above. However, in contrast to type I CrGN (anti-GBM antibody disease) without necrosis show evidence of the underlying immune complex GN (e.g., diffuse leukocyte exudation in postinfectious GN or SLE, and mesangial proliferation in IgA nephropathy or Henoch-Schönlein purpura). Immunofluorescence shows the characteristic **granular pattern** of immune complex disease, and electron microscopy demonstrates discrete deposits.

#### ***Pauci-Immune (Type III) Crescentic Glomerulonephritis***

*Type III CrGN*, also called *pauci-immune type CrGN*, is defined by the lack of anti-GBM antibodies and no immune complex deposition detectable by immunofluorescence and electron microscopy. Most of these individuals have no detectable antibodies in the serum, which, as we have seen ([Chapter 10](#)), have a role in some vasculitides. If it is a component of a systemic vasculitis such as microscopic polyangiitis or Wegener granulomatosis, CrGN is limited to the kidney and is thus called idiopathic.

#### **Morphology**

Glomeruli show **segmental necrosis** and GBM breaks with resulting crescent formation. Uninvolved segments of glomeruli appear normal without proliferation or prominent immune cell infiltration. However, in contrast to anti-GBM antibody disease, immunofluorescence studies for immune complexes and complement are negative or nearly so, and there are no deposits detectable by electron microscopy.

#### ***Clinical Course***

The onset of RPGN is much like that of the nephritic syndrome except that the oliguria and azotemia sometimes approaching nephrotic range may occur. Some of these persons become anuric and require dialysis and transplantation. The prognosis can be roughly related to the number of crescents: those with fewer crescents have a better prognosis than those with higher percentages of crescents. Plasma exchange benefits those with anti-GBM antibody GN and Goodpasture syndrome.

### **SUMMARY**

#### **Rapidly Progressive Glomerulonephritis**

RPGN is a clinical entity with features of the nephritic syndrome and rapid loss of renal function. It is commonly associated with severe glomerular injury with necrosis and GBM breaks and proliferation of parietal epithelium (crescents). RPGN may be immune mediated when autoantibodies develop to the GBM in anti-GBM antibody disease or when there is immune complex deposition; it can also be pauci-immune, associated with few or no antibodies.

#### **Chronic Glomerulonephritis**

Having discussed various forms of glomerular disease, we should now turn to one of their unfortunate complications, which is also referred to as chronic GN by some, irrespective of whether there has been a preceding acute episode. It is an important cause of end-stage renal disease presenting as chronic renal failure. Among all patients undergoing hemodialysis or renal transplantation, 30% to 50% have the diagnosis of chronic GN.



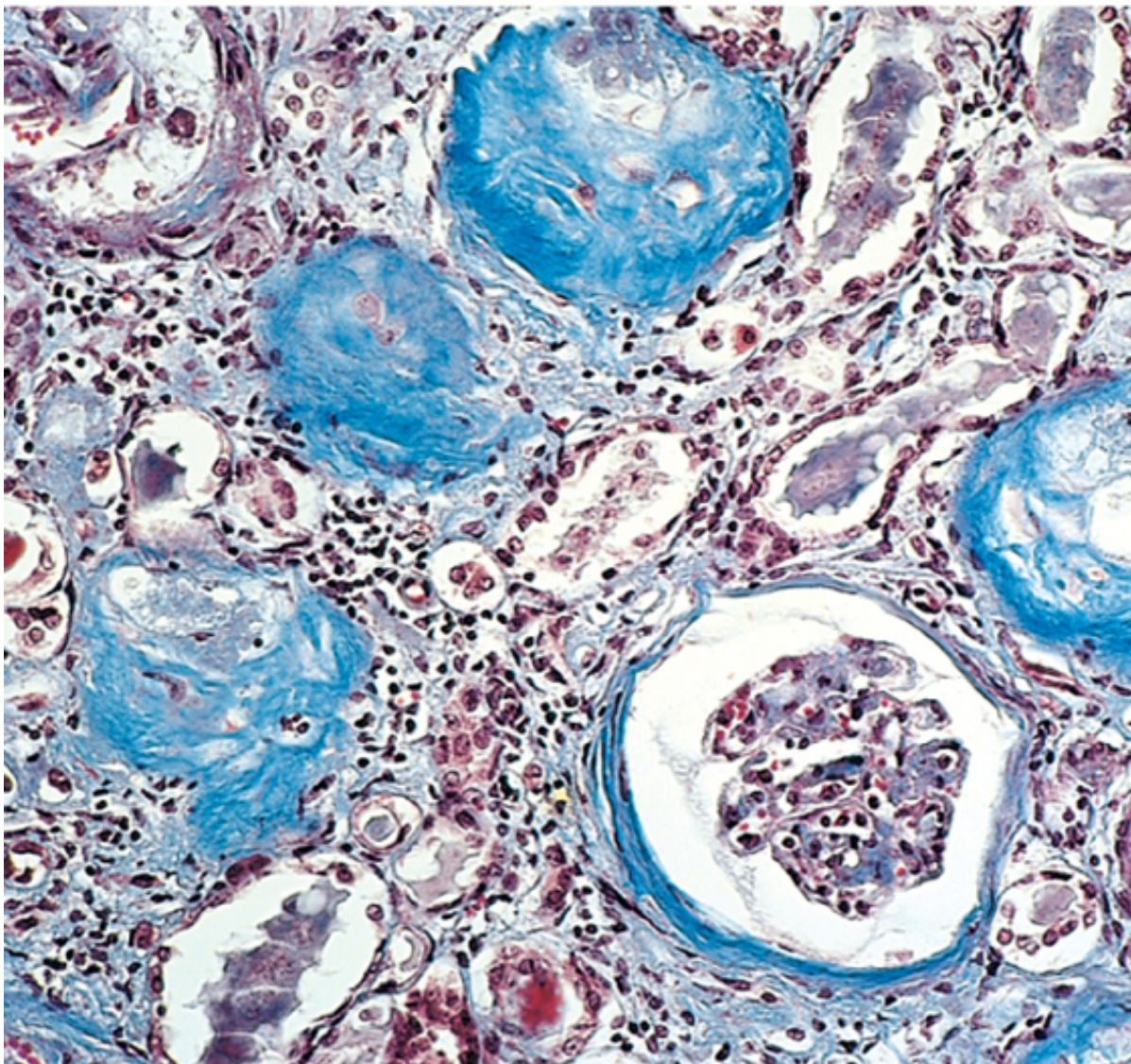
By the time chronic GN is discovered, the glomerular changes are so far advanced that it is difficult to identify the primary lesion. It probably represents the end stage of a variety of entities, prominent among which are the glomerular diseases, and it is impossible to ascertain from such kidneys the nature of the early lesion. It has been estimated that perhaps 20% of cases arise with no history of symptomatic disease. When the disease develops at any age, it is usually first noted in young and middle-aged adults.

### **Morphology**

Classically, the kidneys are **symmetrically contracted** and their surfaces are red-**granular**.

Microscopically, the feature common to all cases is advanced scarring of the glomeruli, leading to a point of complete sclerosis (Fig. 14-13). This **obliteration of the glomeruli** is the end-stage of the disease, and it is impossible to ascertain from such kidneys the nature of the early lesion.

There is also marked **interstitial fibrosis**, associated with atrophy and dropout of the renal cortex, and diminution and loss of portions of the peritubular capillary network. The arteries are frequently thick walled, with narrowed lumina, secondary to hypertension. Occasionally, plasma cell infiltrates are present in the fibrotic interstitial tissue. As damage progresses, it may become difficult to ascertain whether the primary lesion was glomerular or interstitial. Such markedly damaged kidneys are designated "end-stage kidneys".





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Figure 14-13 Chronic GN. A Masson trichrome preparation shows complete replacement of virtually all glomeruli by fibrous tissue. (Kumar et al, Robbins Basic Pathology, 8th ed, Philadelphia, 2008, Elsevier, Inc.)  
Venkatachalam, Department of Pathology, University of Texas Health Sciences Center,

### *Clinical Course*

Most often, chronic GN develops insidiously and is discovered only late in its course, after the onset of renal disease is first detected with the discovery of proteinuria, hypertension, or azotemia on routine laboratory tests. In some individuals the course is punctuated by transient episodes of either the nephritic or the nephrotic syndrome. Patients often seek medical attention for the edema. As the glomeruli become obliterated, the clinical picture of the nephrotic syndrome thus becomes less severe with more advanced disease. Some proteinuria, hypertension, and azotemia. Hypertension is very common, and its effects may dominate the clinical picture. Although microscopic hematuria and bloody urine is infrequent at this late stage.

Without treatment, the prognosis is poor; relentless progression to uremia and death is the rule. The course is variable, however, and 10 years or more may elapse between onset of the first symptoms and the need for kidney transplantation, of course, alter this course and allow long-term survival.



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## DISEASES AFFECTING TUBULES AND INTERSTITIUM

Most forms of tubular injury also involve the interstitium, so the two are discussed together. Under characterized by (1) inflammatory involvement of the tubules and interstitium (interstitial nephritis) leading to *acute tubular necrosis* and *acute renal failure*.

### Tubulointerstitial Nephritis

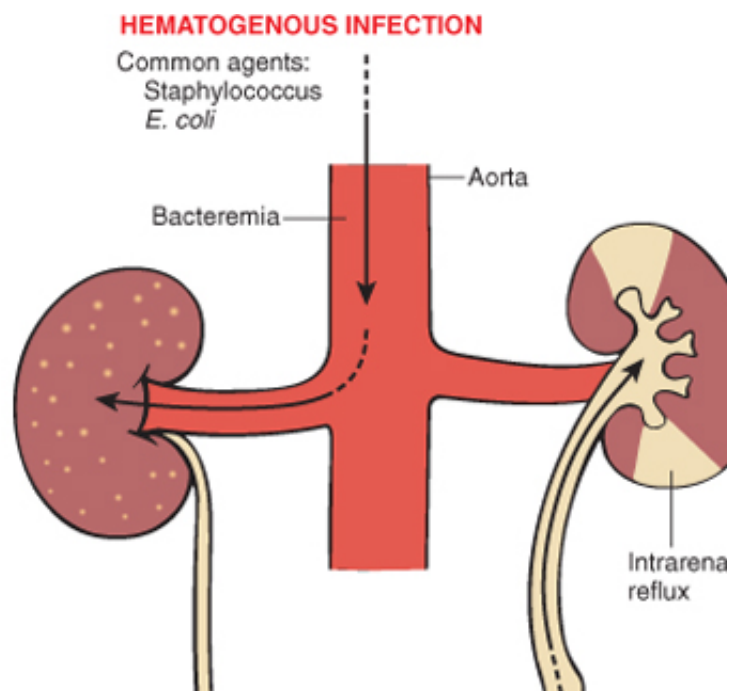
Tubulointerstitial nephritis (TIN) refers to a group of inflammatory diseases of the kidneys that primarily affect the tubules and interstitium. The glomeruli may be spared altogether or affected only late in the course. In most cases of TIN the renal pelvis is prominently involved-hence the more descriptive term *pyelonephritis* (from *pyelo*, "pelvis" generally reserved for cases of TIN that are nonbacterial in origin. These include tubular injury resulting from such as hypokalemia, physical injury such as irradiation, viral infections, and immune reactions. Character of the inflammatory exudate, TIN, regardless of the etiologic agent, can be divided into acute and chronic. In the following section we present pyelonephritis first, followed by other, nonbacterial forms of interstitial nephritis.

#### Acute Pyelonephritis

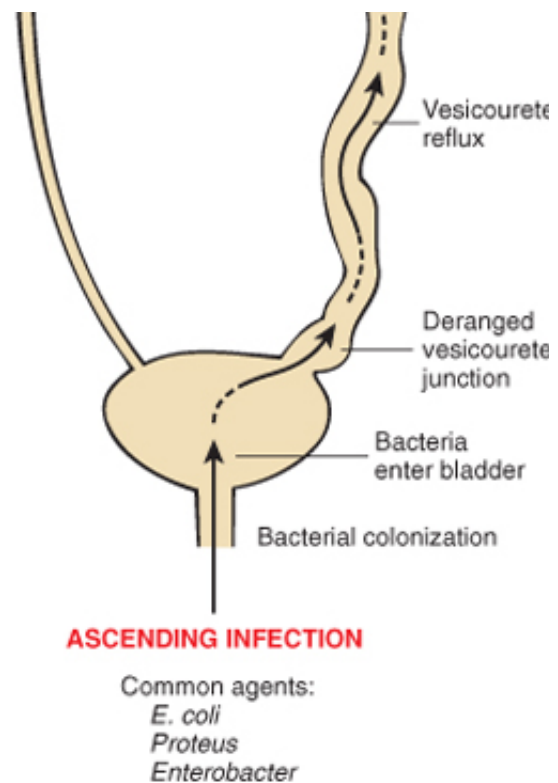
Acute pyelonephritis, a common suppurative inflammation of the kidney and the renal pelvis, is caused by bacteria. It is an important manifestation of urinary tract infection (UTI), which implies involvement of the lower (cystitis) or upper (pyelonephritis) urinary tract, or both. As we will see, the great majority of cases of pyelonephritis are caused by bacteria. The latter, however, may remain localized without extending to involve the kidney. Urinary tract infections are common problems.

#### Pathogenesis

The principal causative organisms are the enteric gram-negative rods. *Escherichia coli* is by far the most common organism. Other organisms are species of *Proteus*, *Klebsiella*, *Enterobacter*, and *Pseudomonas*; these are usually found in persons who undergo urinary tract manipulations or have congenital or acquired anomalies (discussed below). Staphylococci and *Streptococcus faecalis* may also cause pyelonephritis, but they are uncommon.







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 Figure 14-14 Pathways of renal infection. Hematogenous infection results from bacteremic spread. More common combination of urinary bladder infection, vesicoureteral reflux, and intrarenal

There are two routes by which bacteria can reach the kidneys: through the bloodstream (hematogenous spread) and through the urinary tract (ascending infection). Although *hematogenous spread* is the far less common of the two, acute pyelonephritis can be caused by bacteria in the course of septicemia or infective endocarditis (Fig. 14-14). *Ascending infection* is the most important and common route by which the bacteria reach the kidney. The first step in the process seems to be adhesion of bacteria to mucosal surfaces, followed by colonization of the distal urethra. Genetically determined properties of both the urothelium and of bacterial pathogens may facilitate this process. Bacterial fimbriae (proteins that attach to receptors on the surface of urothelial cells), conferring specific adherence, are important. For bacteria to reach the bladder, they must gain access to the bladder, by expansive growth of the colonies and by moving during urethral instrumentation, including catheterization and cystoscopy, which are important predisposing factors for UTIs. In the absence of instrumentation, UTI most commonly affects females. Because of the close proximity of the urethra to the vagina, colonization by enteric bacteria is favored. Furthermore, the short urethra, and trauma to the urethra during intercourse, favor the entry of bacteria into the urinary bladder. Ordinarily, bladder urine is sterile, and remains so, as a result of the bladder mucosa and the flushing action associated with periodic voiding of urine. With outflow obstruction, however, the natural defense mechanisms of the bladder are overwhelmed, setting the stage for infection. Urinary bladder results in incomplete emptying and increased residual volume of urine. In the presence of obstruction, bacteria can multiply undisturbed, without being flushed out or destroyed by the bladder wall. From the bladder, bacteria ascend along the ureters to infect the renal pelvis and parenchyma. Accordingly, UTI is predisposed by urinary tract obstruction, as may occur with benign prostatic hyperplasia and uterine prolapse. Additionally, because of the increased susceptibility to infection and neurogenic bladder dysfunction, which in turn

Although obstruction is an important predisposing factor in the pathogenesis of ascending infection, another important factor is *vesicoureteral reflux* that allows bacteria to ascend the ureter into the pelvis. The normal ureteral orifice acts as a one-way valve that prevents retrograde flow of urine, especially during micturition, when the intravesical pressure is high. In *vesicoureteral reflux*, the vesicoureteral orifice allows the reflux of bladder urine into the ureters, termed *vesicoureteral reflux*. It is usually a congenital defect that results in incompetence of the ureteral orifice. It can be acquired in individuals with a flaccid bladder resulting from spinal cord injury and with neurogenic



sequence of infections that can ascend, resulting from spermecidalgia and from retrograde diabetes. The effect of VUR is similar to that of an obstruction in that after voiding there is residual bacterial growth. Furthermore, VUR affords a ready mechanism by which the infected bladder urine and farther into the renal parenchyma through open ducts at the tips of the papillae (*intrarenal reflux*).

### Morphology

One or both kidneys may be involved. The affected kidney may be normal in size and shape. **Characteristically, discrete, yellowish, raised abscesses are grossly apparent** (Fig. 14-15). They may be widely scattered or limited to one region of the kidney, or form a single large area of suppuration.

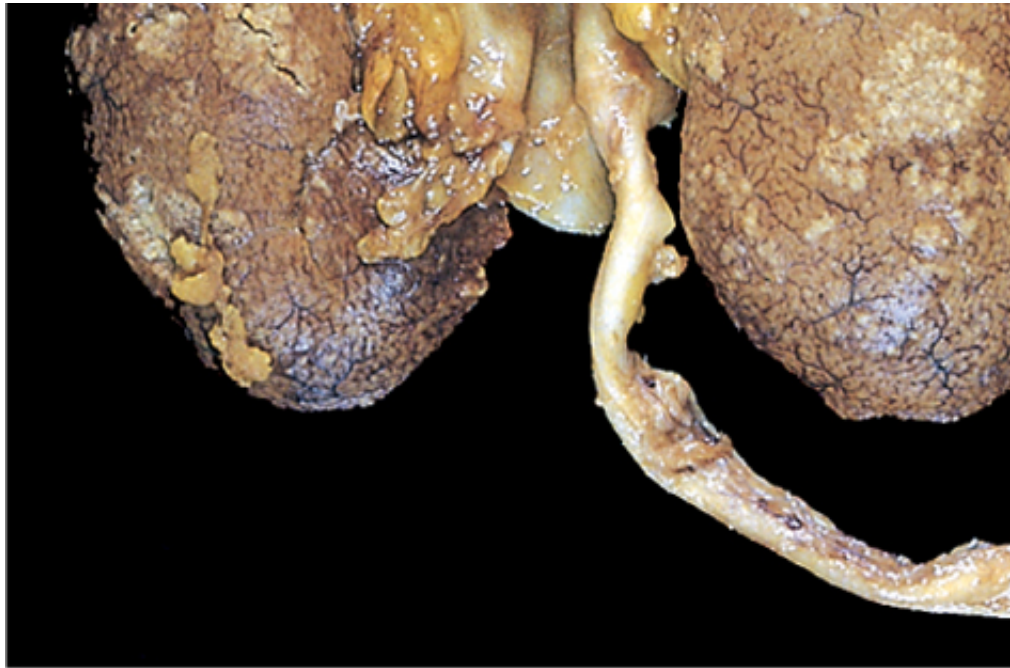
**The characteristic histologic feature of acute pyelonephritis is suppurative inflammation within the renal parenchyma.** In the early stages the suppuration is limited to the interstitial tissue, but later abscesses rupture into tubules. **Large masses of intratubular neutrophils** extend within involved nephrons into the collecting ducts, giving rise to the characteristic "pus in the urine." Typically, the glomeruli are not affected.

When obstruction is prominent, the pus may be unable to drain and thus fills the renal pelvis and ureter, producing pyonephrosis.

A second (and fortunately infrequent) form of pyelonephritis is necrosis of the renal papillae, **papillary necrosis**. This is particularly common among diabetics who develop acute pyelonephritis, but it also complicates acute pyelonephritis when there is significant urinary tract obstruction. Chronic interstitial nephritis associated with analgesic abuse (described below). The combination of ischemic and suppurative necrosis of the tips of the renal pyramids is the pathognomonic gross feature of papillary necrosis: sharply defined gray-white to yellow necrotic areas at the apical two-thirds of the pyramids. One papilla or several or all papillae may be affected. The tips of the papillae show characteristic coagulative necrosis, with surrounding neutrophilic infiltration.

When the bladder is involved in a UTI, as is often the case, **acute or chronic cystitis** is present. In longstanding cases associated with obstruction, the bladder may be grossly hypertrophied with thickened walls, or it may be thinned and markedly distended from retention of urine.





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Figure 14-15 Acute pyelonephritis. The cortical surface is studded with focal pale abscesses, more numerous in the upper pole. The lower pole is relatively unaffected. Between the abscesses there is dark congestion of the cortex.

### *Clinical Course*

Acute pyelonephritis is often associated with predisposing conditions, which were covered in the chapter on urinary tract infections. These include the following:

*Urinary obstruction*, either congenital or acquired. *Instrumentation* of the urinary tract, most commonly catheterization, leads to *reflux*. Increased VUR contributes to the risk of developing pyelonephritis. *Pregnancy*. 4% to 10% of pregnant women have bacteriuria sometime during pregnancy, and 20% to 40% of these eventually develop symptomatic pyelonephritis. *Patient's sex and age*. After the first year of life (when congenital anomalies in males are usually detected), as around age 40 years, infections are much more frequent in females. With increasing age, the development of prostatic hyperplasia and frequent instrumentation. *Preexisting renal disease*. *Diabetes mellitus*, in which acute pyelonephritis is caused by increased susceptibility to infection. *Immunosuppression and immunodeficiency*.

The onset of uncomplicated acute pyelonephritis is usually sudden, with pain at the costovertebral angle, chills, fever, and malaise. *Urinary* findings include pyuria and bacteriuria. In addition, there may be urethral irritation (dysuria, frequency, urgency). Even without antibiotic treatment, the disease tends to be self-limiting. The symptomatic phase of the disease usually lasts no longer than a week, although bacteriuria may persist for several weeks. The disease is usually unilateral, and individuals thus do not develop renal failure because they still have one uninvolved kidney. In the presence of predisposing influences, the disease may become recurrent or chronic, particularly when it is bilateral. Renal necrosis is associated with a much poorer prognosis. These persons have evidence of overwhelming infection. The diagnosis of acute pyelonephritis is established by finding leukocytes ("pus cells") by urinalysis and by culture of the urine.

### **Chronic Pyelonephritis and Reflux Nephropathy**

Chronic pyelonephritis is defined here as a morphologic entity in which predominantly interstitial inflammation and fibrosis of the renal parenchyma is associated with grossly visible scarring and deformity of the pelvicalyceal system. It is a common cause of chronic renal failure. It can be divided into two forms: chronic obstructive pyelonephritis and reflux nephropathy.

### *Chronic Obstructive Pyelonephritis*

We have seen that obstruction predisposes the kidney to infection. Recurrent infections superimposed on obstructive lesions lead to recurrent bouts of renal inflammation and scarring, which eventually cause chronic pyelonephritis, bilateral, as with congenital anomalies of the urethra (posterior urethral valves), resulting in fatal renal failure if not corrected; or unilateral, such as occurs with calculi and unilateral obstructive lesions of the ureter.

### *Chronic Reflux-Associated Pyelonephritis (Reflux Nephropathy)*

This is the more common form of chronic pyelonephritic scarring and results from superimposition of vesicoureteral reflux and intrarenal reflux. Reflux may be unilateral or bilateral; thus, the resultant renal damage may involve one kidney or may involve both and lead to chronic renal insufficiency. Whether VUR causes renal damage (sterile reflux) is uncertain, because it is difficult clinically to rule out remote infections in a person with VUR.

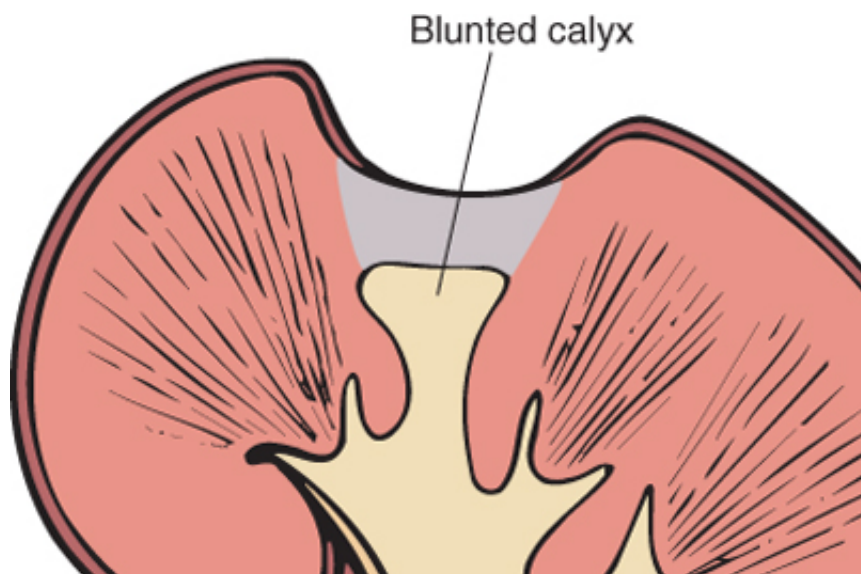
#### **Morphology**

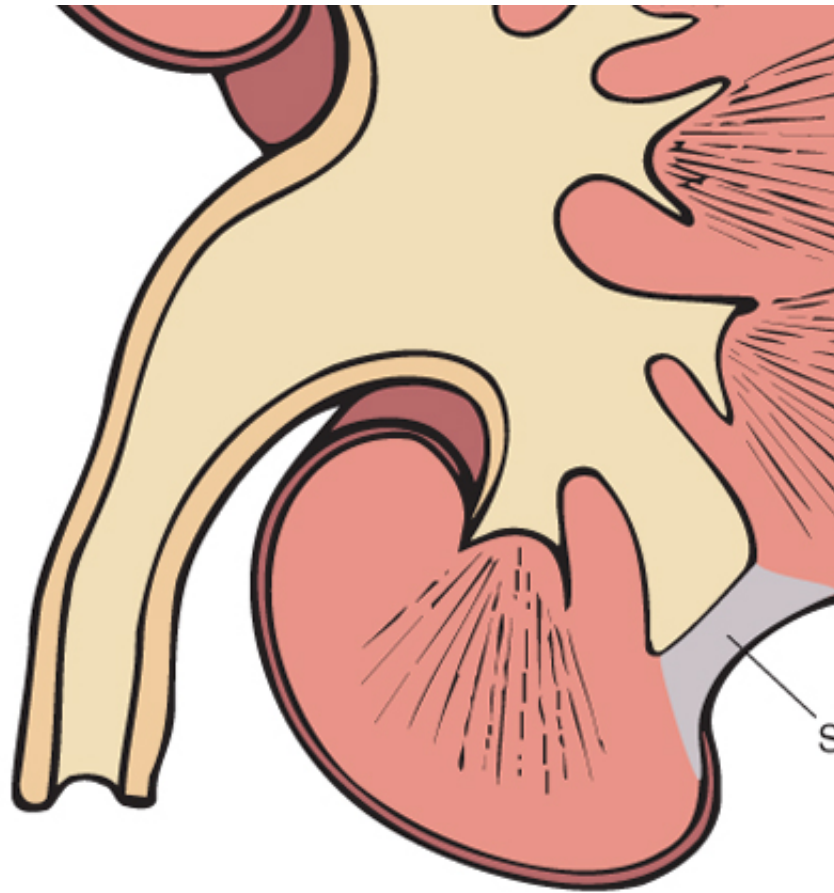
One or both kidneys may be involved, either diffusely or in patches. Even when involved, the kidneys are not equally damaged and therefore are not equally contracted. This is useful for differentiating chronic pyelonephritis from the more symmetrically contracted kidneys of chronic glomerulonephritis (GN). In chronic pyelonephritis is **scarring involving the pelvis or calyces**, or both, leading to papillary necrosis and **calyceal deformities** (Fig. 14-16).

The microscopic changes are largely nonspecific, and similar alterations may be seen in other tubulointerstitial disorders such as analgesic nephropathy. The parenchyma shows

Uneven interstitial fibrosis and an inflammatory infiltrate of lymphocytes, plasma cells, and occasionally neutrophils. Dilation or contraction of tubules, with atrophy of the tubular epithelium. The dilated tubules contain pink to blue, glassy-appearing PAS-positive casts that suggest the appearance of thyroid tissue, hence the descriptive term "thyroidization." Neutrophils are seen within tubules. Chronic inflammatory infiltration and fibrosis of the interstitium. Vascular changes similar to those of benign arteriosclerosis are frequently associated with hypertension. Although glomeruli may be normal, in many cases glomerulosclerosis is seen in areas of better preserved renal parenchyma. Secondary sclerosis caused by maladaptive changes secondary to nephron loss.

### *Clinical Course*





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Figure 14-16 Typical coarse scars of chronic pyelonephritis associated with vesicoureteral reflux. The scars are on the surface of the kidney and are associated with underlying blunted calyces.

Many persons with chronic pyelonephritis come to medical attention relatively late in the course of the disease, often because of the onset of renal insufficiency or because signs of kidney disease are noticed on routine laboratory tests. The disease is often associated with the development of hypertension. Ultrasonography can be used to determine the size and shape of the kidney. A characteristic finding is that the affected kidney is asymmetrically contracted, with some degree of caliectasis (dilation of the calyces). Renal cortical scanning with radioactive technetium can also detect early scars. The absence of significant bacteriuria is not particularly helpful diagnostically; its absence certainly should not rule out the disease. If the disease is bilateral and progressive, tubular dysfunction occurs with loss of concentrating ability, manifested by polyuria and nocturia.

As noted earlier, some persons with chronic pyelonephritis or reflux nephropathy ultimately develop glomerular disease and secondary FSGS. These are associated with proteinuria and eventually contribute to progressive renal insufficiency.

### ***Drug-Induced Interstitial Nephritis***

In this era of antibiotics and analgesics, drugs have emerged as important causes of renal injury. The following section discusses some of the more common drug-induced renal injuries.

#### ***Acute Drug-Induced Interstitial Nephritis***

This is an adverse reaction to any of an increasing number of drugs. Acute TIN most frequently occurs with antibiotics (e.g., **ampicillin**<sup>®</sup>), other synthetic antibiotics (**rifampin**<sup>®</sup>), diuretics (thiazides), nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., phenindione, cimetidine).

#### ***Pathogenesis***

Many features of the disease suggest an immune mechanism. Clinical evidence of hypersensitivity reactions, such as eosinophilia and rash, the information that the onset of nephropathy is not dose related, and the rapid response to corticosteroids support this view.



exposure to the same or a cross-reactive drug. Serum IgE levels are increased in some persons, mononuclear or granulomatous infiltrate, together with positive skin tests to drugs, suggests a T cell reaction.

The most likely sequence of pathogenetic events is that the drugs act as haptens that, during secretion of cytoplasmic or extracellular component of tubular cells and become immunogenic. The resultant T cell IgE- and cell-mediated immune reactions to tubular cells or their basement membranes.

### **Morphology**

The abnormalities in drug-induced nephritis are in the interstitium, which shows peritubular infiltration by mononuclear cells, principally lymphocytes and macrophages (Fig. 14-14). Neutrophils may be present, often in large numbers. With some drugs (e.g., methicillin), interstitial non-necrotizing granulomas with giant cells may be seen. The glomeruli are usually normal, except in cases caused by nonsteroidal anti-inflammatory agents when the hyperplasia of podocytes and podocyte foot process effacement (MCD-like lesion), and the nephrotic syndrome (Fig. 14-15) may be seen.

### *Clinical Course*

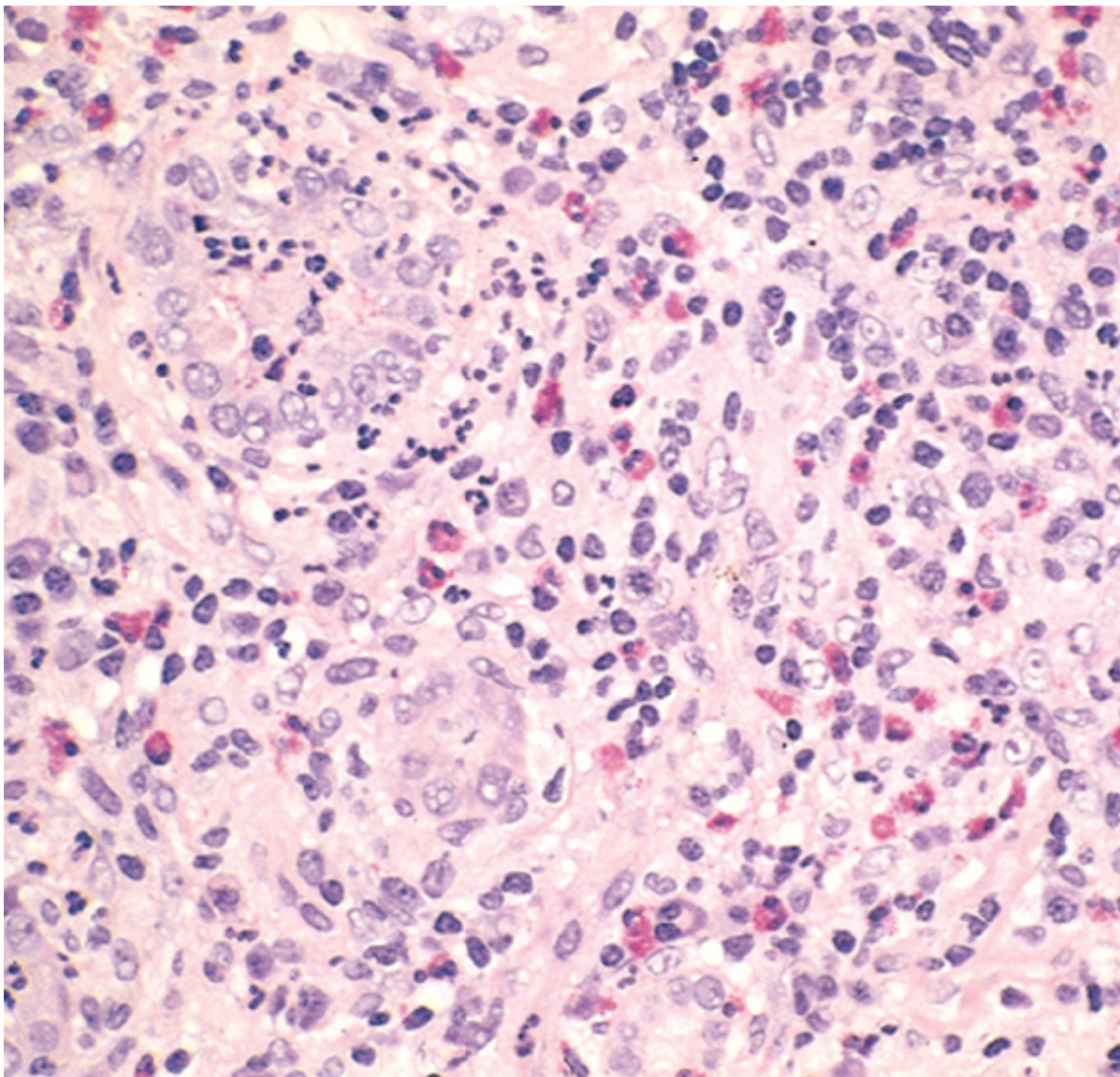


Figure 14-17 Drug-induced interstitial nephritis, with prominent eosinophilic and mononuclear infiltrate. (Courtesy Brigham and Women's Hospital, Boston, Massachusetts.)

The disease begins about 15 days (range, 2-40 days) after exposure to the drug and is characterized by a transient, a rash in about 25% of persons, and renal abnormalities. Renal findings include hematuria and leukocyturia (sometimes including eosinophils). A rising serum creatinine or acute renal failure with oliguria occurs in some cases, particularly in older patients. It is important to recognize drug-induced renal failure, because it is often followed by recovery, although it may take several months for renal function to return to normal.

### Analgesic Nephropathy

Individuals who consume large quantities of analgesics may develop chronic interstitial nephritis, papillary necrosis. Although at times ingestion of single types of analgesics has been incriminated, most patients consume mixtures containing some combination of phenacetin, aspirin<sup>®</sup>, acetaminophen<sup>®</sup>, caffeine, and acetaminophen<sup>®</sup> are the major culprits. While they can cause renal disease in apparently healthy individuals, it seems to be a necessary precursor to analgesic-induced renal failure.

### Pathogenesis

The pathogenesis of the renal lesions is not entirely clear. Papillary necrosis is the initial event, and renal parenchyma is a secondary phenomenon. Acetaminophen<sup>®</sup>, a phenacetin metabolite, injures the renal papilla by oxidative damage. The ability of aspirin<sup>®</sup> to inhibit prostaglandin synthesis suggests that this drug may be inhibiting the vasodilatory effects of prostaglandin and predisposing the papilla to ischemia. Thus, a combination of direct toxic effects of phenacetin metabolites as well as ischemic injury to both the papilla and the renal parenchyma is likely.

### Morphology

The necrotic papillae appear yellowish brown, as a result of the accumulation of brown pigments of phenacetin and other lipofuscin-like pigments. Later on, the papillae may shrivel, become atrophic, and fall into the pelvis. Microscopically, the papillae show coagulative necrosis associated with preservation of tubular outlines. Foci of dystrophic calcification may occur in the necrotic papillae. The cortex drained by the necrotic papillae shows tubular atrophy, interstitial scarring, and glomerular sclerosis. Small vessels in the papillae and urinary tract submucosa exhibit characteristic PAS-positive basement membrane thickening.

### Clinical Course

Common clinical features of analgesic nephropathy include chronic renal failure, hypertension, and anemia. Hematuria and proteinuria may result from damage to red cells by phenacetin metabolites. Cessation of analgesic intake may stabilize the renal function. A complication of analgesic abuse is the increased incidence of transitional-cell carcinoma of the renal pelvis, which may survive the renal failure.

## SUMMARY

### Tubulointerstitial Nephritis

Inflammatory diseases primarily involving the renal tubules and interstitium. Acute tubulointerstitial nephritis is caused either by ascending infection as a result of reflux, hematogenous spread of bacteria; chronic tubulointerstitial nephritis is characterized by tubular atrophy and interstitial fibrosis, sometimes with papillary necrosis. Chronic pyelonephritis is associated with urinary obstruction or reflux; results in scarring of the involved renal parenchyma and renal insufficiency. Drug-induced interstitial nephritis is an IgE- and T cell-mediated disease; characterized by interstitial inflammation, often with abundant eosinophils and edema. Analgesic nephropathy is the result of consumption of large amounts of analgesics; may result in papillary necrosis and progressive renal dysfunction.

### Acute Tubular Necrosis (ATN)

ATN is a clinicopathologic entity characterized morphologically by damaged tubular epithelial cells and decreased renal function. *It is the most common cause of acute renal failure.* In acute renal failure, urine flow is less than 0.5 mL per kg per day (oliguria). Other causes of acute renal failure include (1) severe glomerular diseases and (2) severe vascular diseases such as microscopic polyangiitis and thrombotic microangiopathies, (3) acute pyelonephritis, (4) acute drug-induced interstitial nephritis, and (5) diffuse cortical necrosis. Here, the causes of acute renal failure are discussed elsewhere in this chapter.

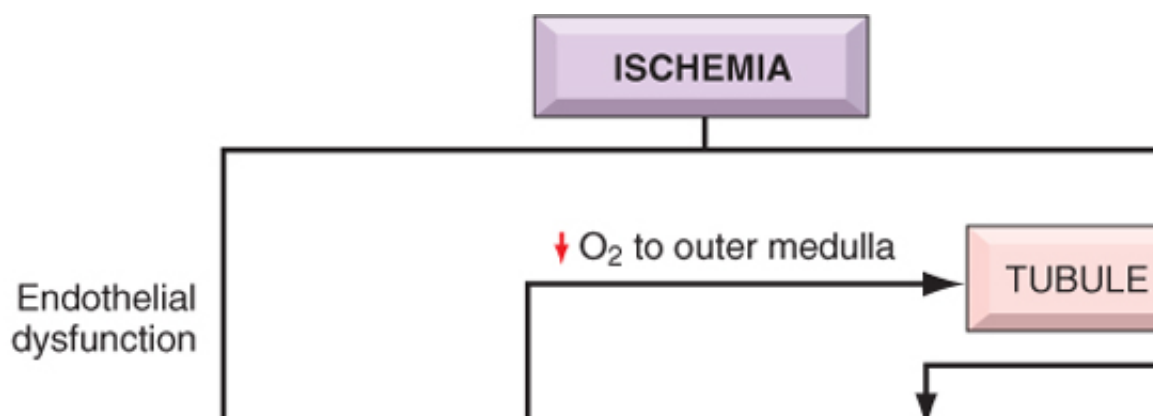
ATN is a reversible renal lesion that arises in a variety of clinical settings. Most of these, ranging from sepsis to shock, have in common a period of inadequate blood flow to the peripheral organs, often in the setting of shock. The pattern of ATN associated with shock is called *ischemic ATN*. Mismatched blood flow, as well as myoglobinuria, also produce a picture resembling ischemic ATN. A second pattern, called *toxic ATN*, is caused by a variety of poisons, including heavy metals (e.g., mercury); organic solvents (e.g., carbon tetrachloride); aminoglycosides, gentamicin and other antibiotics, and radiographic contrast agents. Because of the many precipitants of ATN, its reversibility adds to its clinical importance, because proper management can mean the difference between life and death.

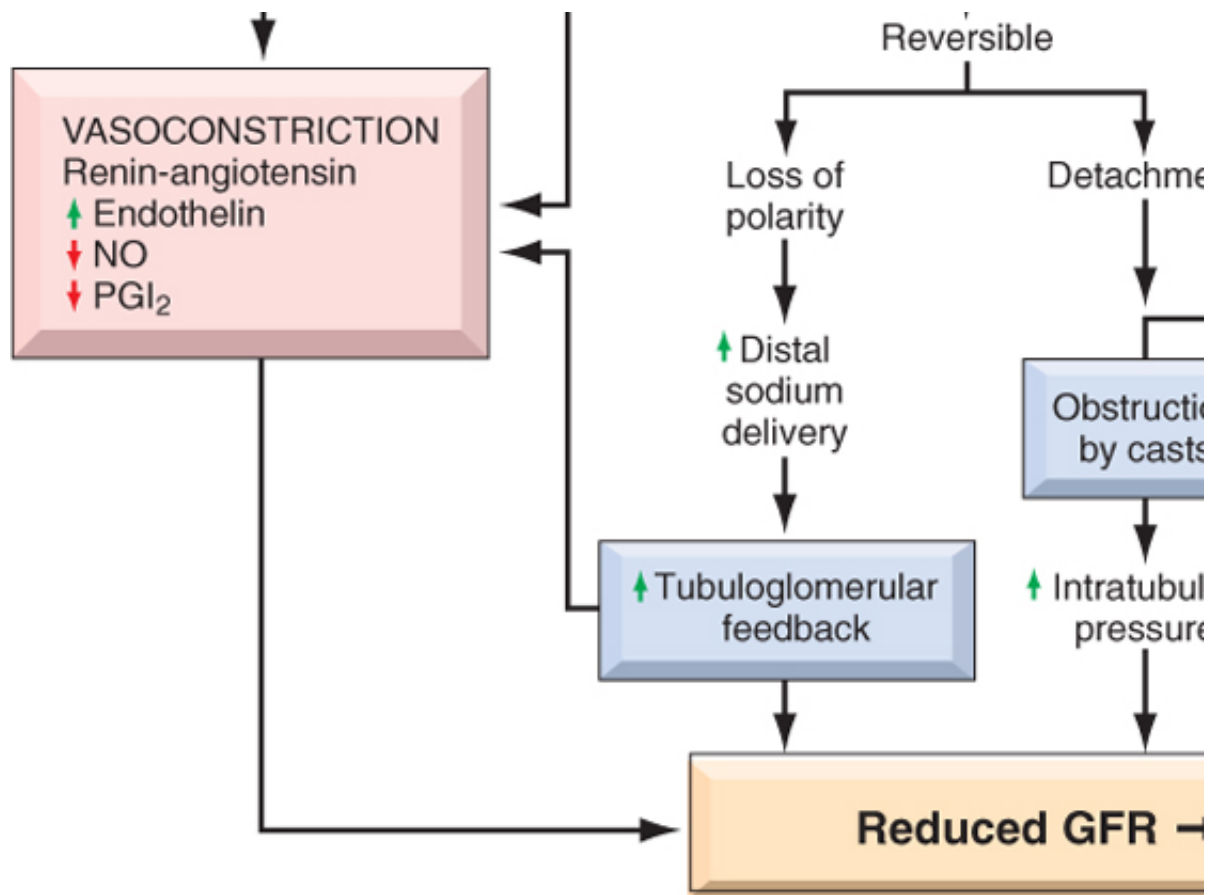
### Pathogenesis

The decisive events in both ischemic and nephrotoxic ATN are believed to be (1) tubular injury and (2) decreased renal blood flow resulting in diminished oxygen and substrate delivery to tubular cells, as depicted in Fig. 14-1.

Tubular epithelial cells are particularly sensitive to anoxia and are also vulnerable to toxins. Severe tubular injury, including a vast electrically charged surface for fluid reabsorption, active transport systems, and the capability for effective concentration. Ischemia causes numerous structural alterations in epithelial cells. The earliest functionally important (but reversible) early event. This leads to redistribution of membrane proteins from the apical to the basolateral surface of tubular cells, resulting in decreased sodium reabsorption by the proximal tubule and decreased sodium delivery to distal tubules. The latter, through a tubuloglomerular feedback system, contributes to the alteration of integrins that anchor tubular cells to their underlying basement membranes results in further damage to the tubules and the resultant tubular debris can block urine outflow and eventually thereby decreasing GFR. Additionally, fluid from the damaged tubules could leak into the interstitium, increasing interstitial pressure and collapse of the tubules. Ischemic tubular cells also express chemokines, cytokines, and selectins that recruit and immobilize leukocytes that can participate in tissue injury.

Ischemic renal injury is also characterized by severe hemodynamic alterations that cause reduced renal blood flow, *vasoconstriction*, which results in both reduced glomerular plasma flow and reduced oxygen delivery to the outer medulla (thick ascending limb and straight segment of the proximal tubule) (see Fig. 14-2). Vasoconstrictor pathways have been implicated in this phenomenon (e.g., renin-angiotensin, thromboxane, and endothelin). Some triggered by the increased distal sodium delivery, the current opinion is that vasoconstriction is a *secondary injury*, leading to increased release of the endothelial vasoconstrictor *endothelin* and decreased production of *prostaglandins*. Finally, there is also some evidence of a direct effect of ischemia or toxins on the glomerular filtration surface.





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Figure 14-18 Postulated sequence in acute renal failure (see text). NO, nitric oxide; GFR, glomerular filtration rate  
from Brady HR, et al.: Acute renal failure. In Brenner BM [ed]: Brenner and Rector's The Kidney, 5th ed, vol II.

## Morphology

**Ischemic ATN** is characterized by **necrosis of short segments** of the tubules. Most necrosis is in the straight portions of the proximal tubule and the ascending thick limbs, but no or distal tubules is spared. Despite the long-standing nomenclature indicating cell necrosis, necrosis of tubular cells is uncommonly seen in renal biopsy samples from persons with ATN. Instead, there is often a variety of **tubular injuries**, including attenuation of brush borders, blebbing and sloughing of brush borders, vacuolization of cells, and detachment of cells from their underlying basement membranes with sloughing of cells into the urine. A striking feature is the presence of proteinaceous casts in the distal tubules and collecting ducts. They contain Tamm-Horsfall protein (secreted normally by tubular epithelium) along with hemoglobin and other debris. If crush injuries have produced ATN, the casts are composed of myoglobin. The interstitium shows generalized edema along with a mild inflammatory infiltrate consisting of polymorphonuclear leukocytes, lymphocytes, and plasma cells. The histologic picture in **toxic ATN** is basically similar to ischemic ATN. Necrosis is most prominent in the proximal tubule, and the tubular basement membrane is generally spared.

If the patient survives for a week, epithelial regeneration becomes apparent in the tubules. There is increased epithelial covering and mitotic activity in the persisting tubular epithelial cells. Once the basement membrane is destroyed, regeneration is total and complete.

## Clinical Course

The clinical course of ATN is characterized by a rapid onset of renal failure, usually within 1-2 weeks of the inciting event. The clinical course is characterized by a rapid onset of renal failure, usually within 1-2 weeks of the inciting event.



The clinical course of ATN may be divided into initiation, maintenance, and recovery stages. The initiation phase is usually dominated by the inciting medical, surgical, or obstetric event in the ischemic form of ATN. The clinical picture is a slight decline in urine output with a rise in serum creatinine. At this point, oliguria could be expected. A decrease in blood flow to the kidneys.

The *maintenance* phase begins anywhere from the second to the sixth day. Urine output falls markedly per day (oliguria). Sometimes it declines to only a few milliliters per day, but complete anuria is rare. It may persist as long as 3 weeks. The clinical picture is dominated by the signs and symptoms of uremia. In the absence of careful supportive treatment or dialysis, patients may die during this phase. With good care, however, they survive.

The *recovery* is ushered in by a steady increase in urine volume, reaching as much as about 3 L/day. Because tubular function is still deranged, serious electrolyte imbalances may occur during this phase. Patients are vulnerable to infection. For these reasons, about 25% of deaths from ATN occur during this phase.

During the final phase there is a gradual return of the individual's well-being. Urine volume returns to normal. Impairment of the kidneys, particularly of the tubules, may persist for months. With modern methods of treatment, patients with the underlying precipitating problem have a 90% to 95% chance of recovering from ATN.

## **SUMMARY**

### **Acute Tubular Necrosis**

ATN is the most common cause of acute renal failure; its clinical manifestations are oliguria, azotemia, and signs of fluid overload. ATN results from ischemic or toxic injury to renal tissue. It is characterized by intrarenal vasoconstriction resulting in reduced GFR and diminished delivery of oxygen and nutrients to tubular epithelial cells. ATN is characterized morphologically by necrosis of tubular epithelial cells (typically the proximal tubules), proteinaceous casts in distal tubules, and in



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## DISEASES INVOLVING BLOOD VESSELS

Nearly all diseases of the kidney involve the renal blood vessels secondarily. Systemic vascular diseases, such as atherosclerosis and arteritis, also involve renal blood vessels, and often the effects on the kidney are clinically important. The renal blood vessels are intimately involved in the pathogenesis of both essential and secondary hypertension. Here we will discuss the changes in the renal blood vessels in benign and malignant hypertension.

### Benign Nephrosclerosis

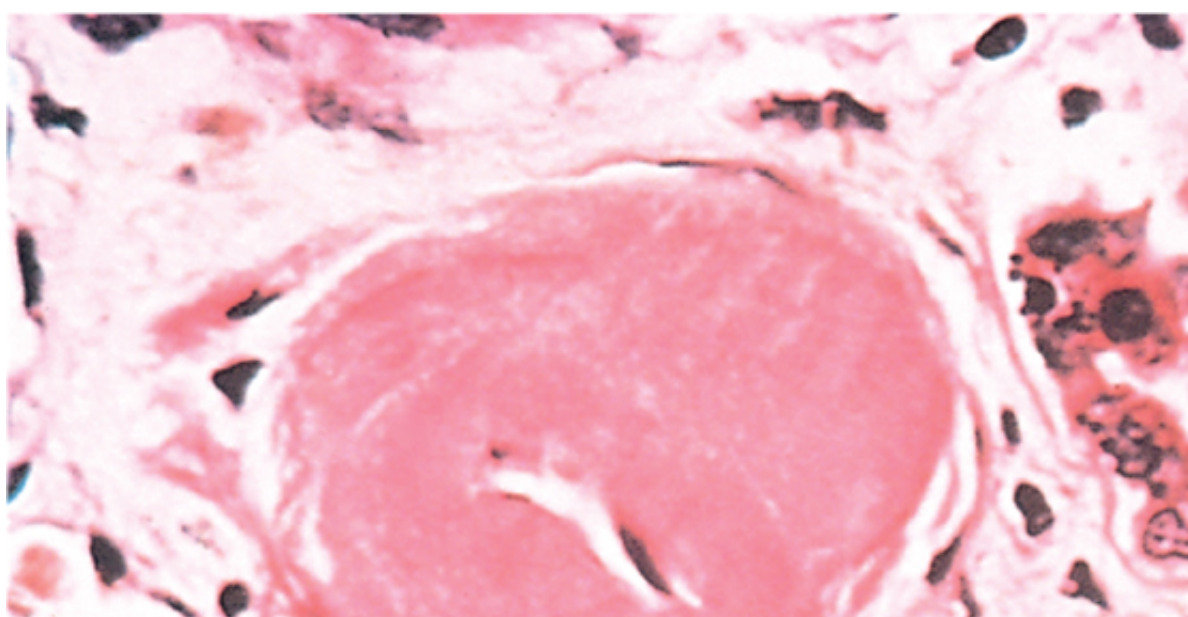
*Benign nephrosclerosis*, the term used for the renal changes in benign hypertension, is always associated with some degree of systemic hypertension. Some degree of benign nephrosclerosis, albeit mild, is present at autopsy in many persons older than 40 years. The severity of the lesions are increased at any age when hypertension or diabetes mellitus are present.

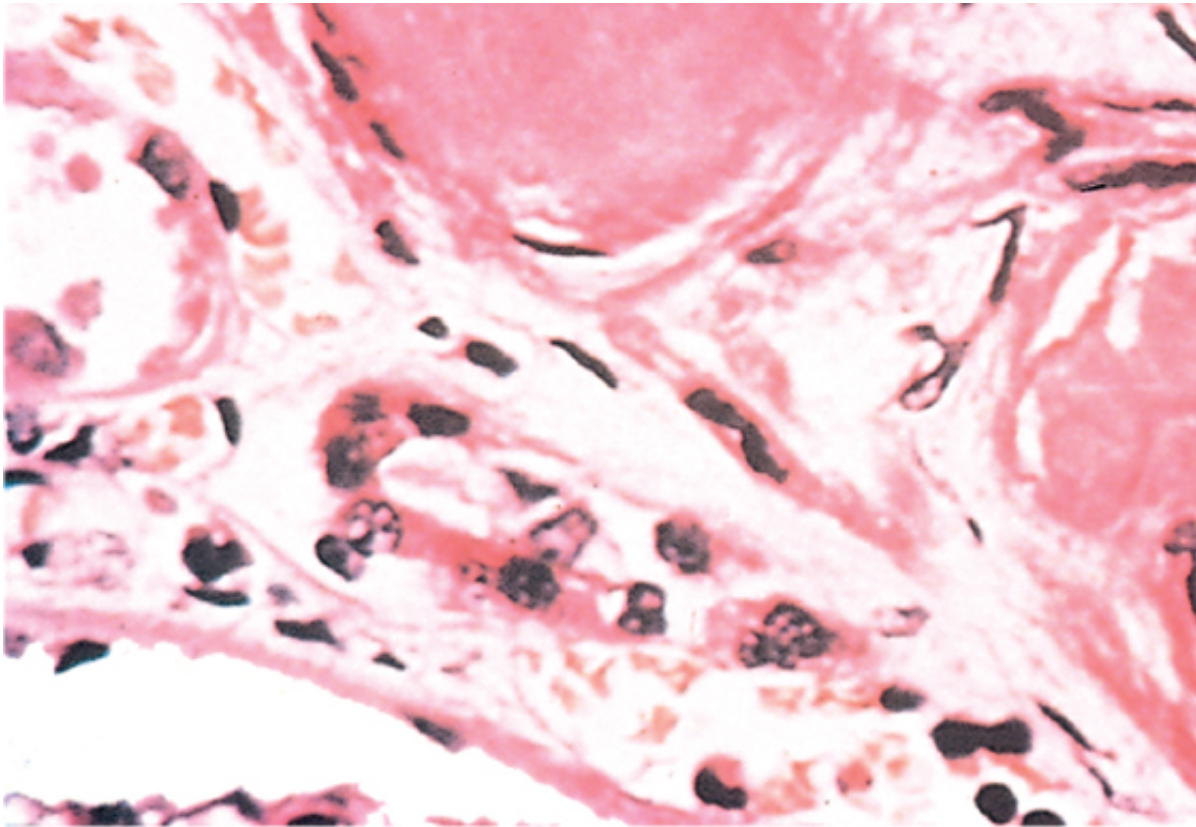
#### *Pathogenesis*

It should be remembered that many renal diseases cause hypertension, which in turn is associated with the development of nephrosclerosis, or a subtle primary microvascular renal injury causes the hypertension, and the sclerosis, is not known. Thus, this renal lesion is often seen superimposed on other primary kidney diseases. In the renal arteries and arterioles are seen in individuals with chronic thrombotic microangiopathies.

#### **Morphology**

Grossly, the kidneys are **symmetrically atrophic**, each weighing 110 to 130 gm, and have a fine granularity that resembles grain leather. Microscopically, the basic anatomic change is the hyaline thickening of the walls of the small arteries and arterioles, known as **hyaline arteriosclerosis**. This is a homogeneous, pink hyaline thickening, at the expense of the vessel lumen, with little cellular detail ([Fig. 14-19](#)). The narrowing of the lumen results in markedly decreased blood flow through the renal vessels and thus produces ischemia in the organ served. All structures of the kidney are affected. In advanced cases of benign nephrosclerosis the glomerular tufts may become globally sclerotic, and tubular atrophy and interstitial fibrosis are present. Often there is a scant interstitial inflammatory infiltrate. In larger blood vessels (interlobar and arcuate arteries) show reduplication of internal elastic lamina, fibrous thickening of the media (**fibroelastic hyperplasia**) and the subintima.





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 Figure 14-19 Benign nephrosclerosis. High-power view of two arterioles with hyaline deposition, marked thickening  
 Dr. M. A. Venkatachalam, Department of Pathology, University of Texas Health Sciences Ce

#### *Clinical Course*

This renal lesion alone rarely causes severe damage to the kidney except in susceptible population may lead to uremia and death. However, all persons with this lesion usually show some functional concentrating ability or a variably diminished GFR. A mild degree of proteinuria is a frequent finding

#### **Malignant Hypertension and Malignant Nephrosclerosis**

Malignant hypertension is far less common in the United States than benign hypertension and occurs at elevated blood pressure. It may arise *de novo* (i.e., without preexisting hypertension), or it may appear in the setting of preexisting hypertension. In less developed countries, it occurs more commonly.

#### *Pathogenesis*

The basis for this turn for the worse in hypertensive subjects is unclear, but the following sequence seems to be some form of vascular damage to the kidneys. This most commonly results from long-standing hypertension, which causes eventual injury to the arteriolar walls. The result is increased permeability of the small vessels to fibrinogen and other plasma proteins, leading to endothelial injury, and platelet deposition. This leads to the appearance of *fibrinoid necrosis* of arterioles, which may result in intravascular thrombosis. Mitogenic factors from platelets (e.g., platelet-derived growth factor) and hyperplasia of vessels, resulting in the *hyperplastic arteriolosclerosis* typical of malignant hypertension. In thrombotic microangiopathies (see below) and further narrowing of the lumina. The kidneys become involved. In the setting of involvement of the renal afferent arterioles, the renin-angiotensin system receives a powerful stimulus. In *malignant hypertension* have *markedly elevated levels of plasma renin*. This then sets up a self-perpetuating cycle of intrarenal vasoconstriction, and the attendant renal ischemia perpetuates renin secretion. Aldosterone retention undoubtedly contributes to the elevation of blood pressure. The consequences of the malignant hypertension on the blood vessels throughout the body are known as *malignant arteriolosclerosis*, and the renal disorder is known as *nephrosclerosis*.



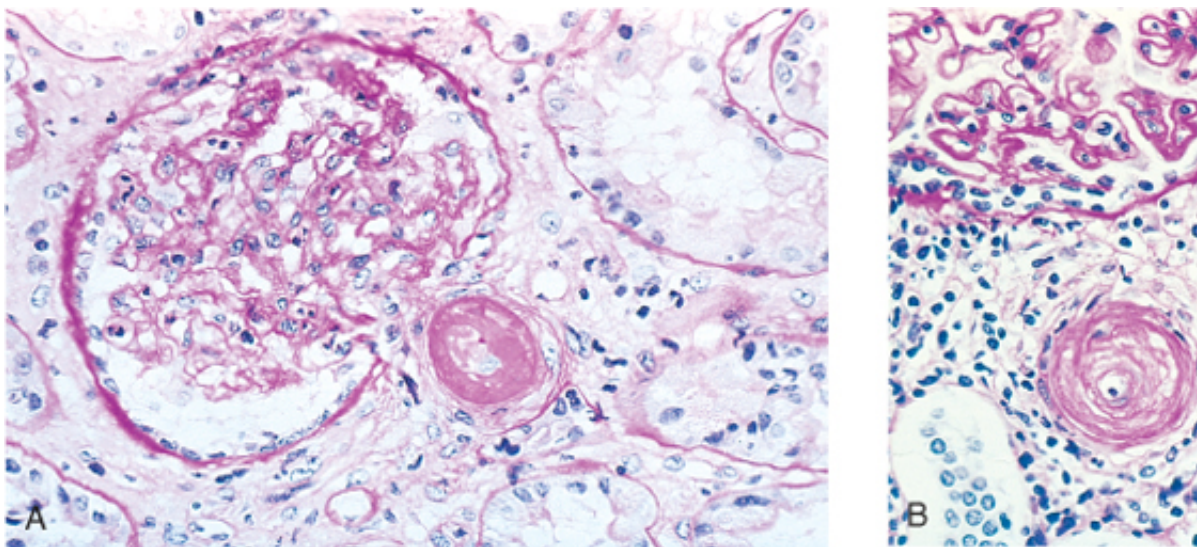
### Morphology

The kidney may be essentially normal in size or slightly shrunken, depending on the hypertensive disease. Small, **pinpoint petechial hemorrhages** may appear on rupture of arterioles or glomerular capillaries, giving the kidney a peculiar, **flea-bitten**

The microscopic changes reflect the pathogenetic events described earlier. Damage manifested as **fibrinoid necrosis** of the arterioles (Fig. 14-20A). The vessel walls have a granular eosinophilic appearance masking underlying detail. In the interlobular arteries, proliferation of intimal cells produces an onion-skin appearance (Fig. 14-20B). This concentric arrangement of cells whose origin is believed to be intimal smooth muscle is not finally settled. This lesion, called **hyperplastic arteriosclerosis**, causes narrowing of medium and small arteries, to the point of total obliteration. Necrosis may also involve glomeruli within the glomeruli as well as necrotic arterioles. Similar lesions are seen in periorbital microangiopathies.

### Clinical Course

The full-blown syndrome of malignant hypertension is characterized by diastolic pressures greater than 130 mm Hg, encephalopathy, cardiovascular abnormalities, and renal failure. Most often, the early symptoms are related to **high blood pressure** and include headache, nausea, vomiting, and visual impairment, particularly the development of retinal hemorrhages. At the onset of rapidly mounting blood pressure there is marked proteinuria and microscopic hematuria, but no significant alteration in renal function. Soon, however, **renal failure** makes its appearance. Malignant hypertension is a medical emergency that requires prompt and aggressive antihypertensive therapy before irreversible renal damage occurs. Without treatment, patients survive at least 5 years, and further progress is still being made. Ninety percent of deaths are caused by cerebral hemorrhage or cardiac failure.



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Figure 14-20 Malignant hypertension. **A**, Fibrinoid necrosis of afferent arteriole (PAS stain). **B**, Hyperplastic arteriosclerosis (PAS stain). Dr. Michael J. Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.

### Thrombotic Microangiopathies

As described in Chapter 12, this term describes lesions seen in various clinical syndromes, characterized by thrombosis in the microcirculation and clinically by **microangiopathic hemolytic anemia**, **thrombocytopenia**, and **renal failure**. Common diseases that cause lesions of thrombotic microangiopathy include (1) childhood hemolytic uremic syndrome (HUS), (2) various forms of adult HUS, and (3) thrombotic thrombocytopenic purpura (TTP).

Pathogenesis



### *Pathogenesis*

Although clinically overlapping, HUS and TTP are pathogenetically distinct. Central to the pathogenesis is platelet *activation*, with resultant intravascular thrombosis. TTP is now known to be caused by an acquired deficiency of von Willebrand factor (vWF) multimers, or more rarely, an inherited defect as seen in familial TTP (Chapman). The acquired deficiency of vWF is caused by a deficiency of vWF protease referred to as ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs).

*Childhood HUS* is the best characterized of the renal syndromes. As many as 75% of cases follow infection with *E. coli*, such as occurs in epidemics caused by ingestion of infected ground meat (e.g., *E. coli* O157:H7). The pathogenesis of this syndrome is related to the effects of Shiga toxin, which enters the circulation. Renal glomerular endothelial cells are targets of this toxin because the cells express the toxin receptor. Shiga toxin has multiple effects on the endothelium, including increased adhesion of leukocytes, increased production of endothelial nitric oxide<sup>2</sup> (both favoring vasoconstriction), and (in the presence of cytokines, such as IL-1 and IL-6) increased endothelial damage. The toxin also gains entry to the cells and directly causes cell death. The resultant endothelial injury is most prominent in glomerular capillaries, afferent arterioles, and interlobular arteries, as well as in the small intestine, leading to characteristic thrombotic microangiopathy.

Approximately 10% of the cases of HUS in children are not preceded by diarrhea caused by Shiga toxin-producing *E. coli*; in these patients there is mutational inactivation of complement regulatory proteins (e.g. factor H), with subsequent complement activation following minor vascular injuries. This then promotes the formation of thrombi.

### **Morphology**

In childhood HUS, there are lesions of classic **thrombotic microangiopathy** with thrombi predominantly involving glomeruli, and extending into arterioles and larger arteries. Endothelial cell necrosis may be present. Morphologic changes in glomeruli resulting from endothelial injury include narrowing of the subendothelial space in glomerular capillaries, duplication or splitting of GBM, and endothelial cell swelling with mesangial disintegration. Chronically, scarring of glomeruli may develop.

### *Clinical Course*

Typically, childhood HUS is characterized by the sudden onset, usually after a gastrointestinal or respiratory infection, of manifestations (especially hematemesis and melena), severe oliguria, hematuria, microangiopathic changes in peripheral blood (schistocytes), and prominent neurologic changes. *This disease is one of the main causes of acute renal failure in children.* If managed properly with dialysis, most patients recover in a matter of weeks. The long-term (15- to 20-year) outcome is usually favorable, because about 25% of children eventually develop renal insufficiency due to chronic kidney disease.

## **SUMMARY**

### **Vascular Diseases of the Kidney**

**Benign nephrosclerosis:** Progressive, chronic renal damage associated with hyaline arteriosclerosis and narrowing of vascular lumen. **Malignant nephrosclerosis:** Acute renal injury associated with fibrinoid necrosis and hyperplasia of smooth muscle cells in the arterial wall. **Thrombotic microangiopathy:** Disorders characterized by fibrin thrombi in glomeruli and small vessels resulting from endothelial injury. **Childhood hemolytic uremic syndrome** is caused by endothelial injury by an enterohemorrhagic *E. coli* (EHEC) infection. **Thrombotic thrombocytopenic purpura** is caused by defects in von Willebrand factor cleaving protease, with platelet consumption.





## CYSTIC DISEASES OF THE KIDNEY

Cystic diseases of the kidney are a heterogeneous group comprising hereditary, developmental and acquired diseases. As a group, they are important for several reasons: (1) they are reasonably common and often present a diagnostic challenge to radiologists, and pathologists; (2) some forms, such as adult polycystic disease, are major causes of end-stage renal disease and occasionally be confused with malignant tumors. *An emerging theme in the pathophysiology of the cystic diseases is that the underlying defect is in the cilia-centrosome complex of tubular epithelial cells.* Such defects may interfere with normal cell maturation, resulting in cyst formation. Here we briefly mention simple cysts, the most common form of kidney disease.

### Simple Cysts

These generally innocuous lesions occur as multiple or single cystic spaces that vary widely in diameter; translucent; lined by a gray, glistening, smooth membrane; and filled with clear fluid. Microscopically, they are composed of a single layer of cuboidal or flattened cuboidal epithelium, which in many instances is usually confined to the cortex. Rarely, massive cysts as large as 10 cm in diameter are encountered.

Simple cysts are a common post-mortem finding that has no clinical significance. The main importance is in distinguishing them from kidney tumors, when they are discovered either incidentally or because of hemorrhage and contrast enhancement. In contrast to renal tumors, renal cysts have smooth contours, are almost always avascular, and give no enhancement on ultrasonography.

*Dialysis-associated acquired cysts* occur in the kidneys of patients with end-stage renal disease who are on long-term dialysis. They are present in both cortex and medulla and may bleed, causing hematuria. Occasionally, renal calculi may arise in the walls of these cysts.

### Autosomal Dominant (Adult) Polycystic Kidney Disease

Adult polycystic kidney disease is characterized by multiple expanding cysts of both kidneys that replace the normal renal parenchyma. It is seen in approximately 1 in 500 to 1000 persons and accounts for 10% of cases of end-stage renal disease. It is genetically heterogeneous. It can be caused by inheritance of one of at least two autosomal dominant genes. In 85% to 90% of families, *PKD1*, the defective gene is on the short arm of chromosome 16. This gene encodes a complex cell membrane-associated protein, called polycystin-1, that is mainly extracellular.

### Pathogenesis

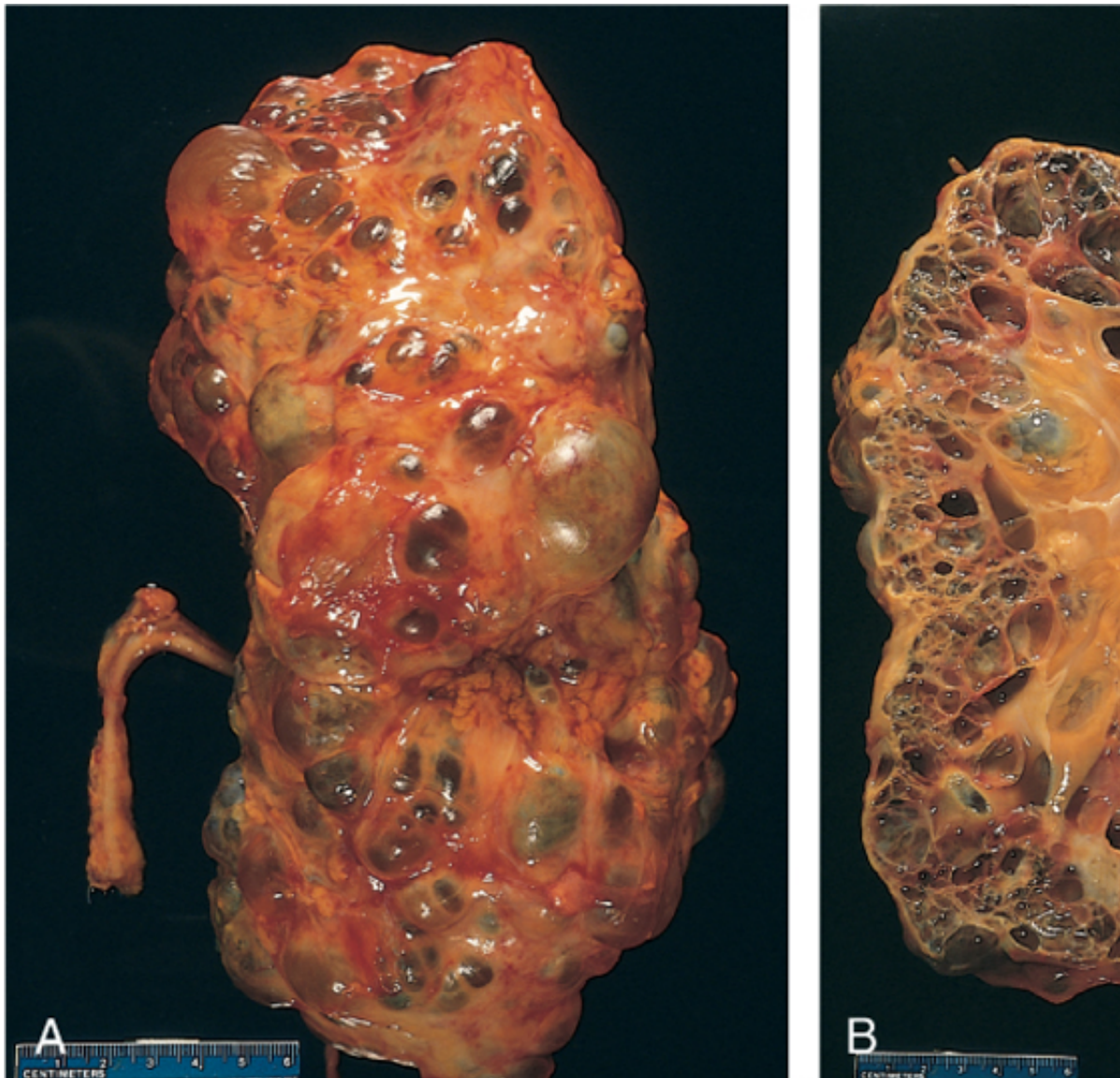
The polycystin molecule has regions of homology with proteins involved in cell-cell or cell-matrix adhesion (e.g., integrins, collagen, laminin, and fibronectin). It also has several other domains including those that can bind calcium. The exact mechanism by which mutations in this protein cause cyst formation is at present unclear, but it is thought that the result is a failure to regulate cell proliferation, leading to alterations in proliferation, adhesion, differentiation, and matrix production by tubular epithelial cells. Polycystins have also been localized in tubular cilia, like the nephrocystins linked to medullary cystic degeneration. It is interesting to note that whereas germ-line mutations of the *PKD1* gene are present in all renal tubules, somatic mutations develop in only some tubules. This is most likely due to loss of both alleles of *PKD1*. Thus, as with the *RET* gene, a "somatic hit" is required for expression of the disease. The *PKD2* gene, implicated in 10% to 15% of cases, encodes *polycystin 2*, a smaller, 110-kD protein. Polycystin 2 is thought to function as a calcium-binding protein. Structurally distinct, polycystins 1 and 2 are believed to act together by forming heterodimers. They produce essentially the same phenotype, although patients with *PKD2* mutations have a slower rate of disease progression than patients with *PKD1* mutations.

### Morphology

In autosomal dominant adult polycystic kidney disease, the kidney may reach enormous size. In some cases, kidneys weighing up to 4 kg for each kidney have been recorded. These **very large kidneys** are really masses of cysts extending into the pelvis. On gross examination the kidney seems to be composed of a mass of cysts of varying sizes up to 3 or 4 cm in diameter with no intervening parenchyma. The cysts are filled with fluid, which may be clear, turbid, or hemorrhagic (Fig. 14-21).

lined with fluid, which may be clear, turbid, or hemorrhagic (Fig. 14-21).

Microscopic examination reveals some normal parenchyma dispersed among the cysts at any level of the nephron, from tubules to collecting ducts, and therefore they have an epithelial lining. Occasionally, Bowman's capsules are involved in the cyst formation, and intimal tufts may be seen within the cystic space. The pressure of the expanding cysts leads to the atrophy of the intervening renal substance. Evidence of superimposed hypertension or infection is rare. Asymptomatic liver cysts occur in one-third of patients.



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Figure 14-21 Autosomal dominant adult polycystic kidney, viewed from the external surface (A) and bisected (B) with numerous dilated cysts.

#### Clinical Course

Polycystic kidney disease in adults usually *does not produce symptoms until the fourth decade*, but although small cysts start to develop in adolescence. The most common presenting complaint is *flank pain*. Acute distention of a cyst, either by intracystic hemorrhage or by obstruction, may cause excruciating

drawn to the lesion by palpation of an abdominal mass. *Intermittent gross hematuria* commonly occurs because of their deleterious effect on already marginal renal function, are *hypertension and urinary proteinuria*. The severity develops in about 75% of persons with this disorder. Saccular aneurysms of the circle of Willis occur in about 30% of patients, and these individuals have a high incidence of subarachnoid hemorrhage.

Although the disease is ultimately fatal, the outlook is generally better than with most chronic renal diseases. The disease is relatively stable and progresses very slowly. End-stage renal failure occurs at about age 50, but the disease is not a renal disorder, and nearly normal life spans are reported. Those who develop renal failure are treated by dialysis or transplantation. Results from uremia or hypertensive complications.

### **Autosomal Recessive (Childhood) Polycystic Kidney Disease**

This rare developmental anomaly is genetically distinct from adult polycystic kidney disease, having a different inheritance pattern, occurs in approximately 1 in 20,000 live births. Perinatal, neonatal, infantile, and juvenile subcategories are defined by the time of presentation and the presence of associated hepatic lesions. All result from mutations in a membrane receptor protein called *fibrocystin*, localized to chromosome 6p. Fibrocystin may be involved in the function of epithelial cells (see below).

#### **Morphology**

In autosomal recessive polycystic kidney disease, **numerous small cysts** in the cortex of the kidney give it a spongelike appearance. Dilated, elongated channels at right angles to the collecting ducts completely replace the medulla and cortex. The cysts have a uniform lining of cuboidal epithelium of origin from the collecting tubules. The disease is invariably bilateral. In almost all cases, there is also **cysts in the liver** as well as proliferation of portal bile ducts.

#### *Clinical Course*

Perinatal and neonatal forms are most common; serious manifestations are usually present at birth, including respiratory distress, hepatic or renal failure. Patients who survive infancy develop liver cirrhosis (congenital hepatic fibrosis) and/or renal failure.

### **Medullary Cystic Disease**

There are two major types of medullary cystic disease: *medullary sponge kidney*, a relatively common form which will not be discussed further, and *nephronophthisis-medullary cystic disease complex*, which is a severe form of renal dysfunction.

Nephronophthisis-medullary cystic disease complex is an under-recognized cause of chronic kidney disease in childhood. Four variants of this disease complex are recognized on the basis of the time of onset: infantile, juvenile, adolescent, and adult. The juvenile form is the most common. Approximately 15% to 20% of individuals with juvenile nephronophthisis have manifestations, which most often appear as retinal abnormalities, including retinitis pigmentosa, the most severe form. Other abnormalities found in some persons include oculomotor apraxia, mental retardation, and liver fibrosis. In aggregate, the various forms of nephronophthisis are now thought to be the most common renal disease in children and young adults.

#### *Pathogenesis*

At least seven gene loci have been identified for this complex, with both autosomal dominant and recessive inheritance. Genes *NPHP1* through *NPHP5* define the infantile, juvenile, and adolescent forms of nephronophthisis. The protein products of *NPHP1* and *NPHP3* through *NPHP5* (nephrocystins 1 and 3-5) are located on the primary cilia of epithelial cells, which in turn has led to a currently attractive hypothesis that ciliary dysfunction causes polycystic kidney disease. However, the normal functions of nephrocystins and their specific roles are unknown. Two genes (*MCKD1* and *MCKD2*), with autosomal dominant transmission, cause medullary cystic disease.

#### **Morphology**

Pathologic features of medullary cystic disease include **small contracted kidneys** in which the tubules lined by flattened or cuboidal epithelium are present, typically at the cortico-medullary junction. The pathologic changes are nonspecific, but most notably they include a chronic tubulointerstitial nephropathy.



tubular atrophy and thickened tubular basement membranes and progressive inter

### *Clinical Course*

The initial manifestations are usually polyuria and polydipsia, a consequence of diminished tubular function. The disease ensues over a 5- to 10-year period. The disease is difficult to diagnose, since the cysts are too small to be seen with radiologic imaging. Adding to this difficulty, cysts may not be apparent on biopsy if the junction is not well sampled. A positive family history and unexplained chronic renal failure in your family suggest medullary cystic disease.

### **SUMMARY** **Cystic Diseases**

*Adult polycystic kidney disease* is an autosomal dominant disease caused by mutations in the gene encoding polycystin-1 or -2; it accounts for about 10% of cases of chronic renal failure. The kidneys are very large and contain many cysts. *Autosomal recessive (childhood) polycystic kidney disease* is caused by mutations in the gene encoding fibrocystin; it is less common than the autosomal dominant form and is strongly associated with liver abnormalities; kidneys contain numerous small cysts. *Medullary cystic disease* is being increasingly recognized as a cause of chronic renal failure in adults; it has a complex inheritance, and is associated with mutations in several genes encoding epithelial cell proteins called nephrocystins that may be involved in ciliary function. The kidneys are contracted and contain multiple small cysts.



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## URINARY OUTFLOW OBSTRUCTION

### Renal Stones

*Urolithiasis* is calculus formation at any level in the urinary collecting system, but most often the calculi arise in the kidney. They occur frequently, as is evidenced by the finding of stones in about 1% of all autopsies. Symptomatic urolithiasis is more common in men than in women. A familial tendency toward stone formation has long been recognized.

#### Pathogenesis

About 80% of renal stones are composed of either calcium oxalate or calcium oxalate mixed with calcium phosphate. Another 10% are composed of magnesium ammonium phosphate, and 6% to 9% are either uric acid or cystine stones. In all cases, there is an organic matrix of mucoprotein that makes up about 2.5% of the stone by weight ([Table 14-4](#)).

**Table 14-4. Prevalence of Various Types of Renal Stones**

Stone	Percentage of All Stones
<b>Calcium Oxalate and/or Calcium Phosphate</b>	<b>80</b>
Idiopathic hypercalciuria (50%)	
Hypercalcemia and hypercalciuria (10%)	
Hyperoxaluria (5%)	
Enteric (4.5%)	
Primary (0.5%)	
Hyperuricosuria (20%)	
No known metabolic abnormality (15% to 20%)	
<b>Struvite (Mg, NH<sub>3</sub>, Ca, PO<sub>4</sub>)</b>	<b>10</b>
Renal infection	
<b>Uric Acid</b>	<b>6-7</b>
Associated with hyperuricemia	
Associated with hyperuricosuria	
Idiopathic (50% of uric acid stones)	
<b>Cystine</b>	<b>1-2</b>
<b>Others or Unknown</b>	<b>±1-2</b>

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The cause of stone formation is often obscure, particularly in the case of calcium-containing stones. Probably involved is a confluence of predisposing conditions. *The most important cause is increased urine concentration of the stone's constituents, so that it exceeds their solubility in urine (supersaturation).* As shown in [Table 14-4](#), 50% of patients who develop *calcium stones* have hypercalciuria that is not associated with hypercalcemia. Most in this group absorb calcium from the gut in excessive amounts (absorptive hypercalciuria) and promptly excrete it in the urine, and some have a primary renal defect of calcium reabsorption (renal hypercalciuria). In 5% to 10% of persons with this diagnosis there is hypercalcemia (due to hyperparathyroidism, vitamin D intoxication, or sarcoidosis) and consequent hypercalciuria. In 20% of this subgroup, there is excessive excretion of uric acid in the urine, which favors calcium stone formation; presumably the urates provide a nidus for calcium deposition. In 5% there is hyperoxaluria or hypercitraturia, and in the remainder there is no known metabolic abnormality. A high urine pH favors crystallization of calcium phosphate and stone formation.

## Stone formation

The causes of the other types of renal stones are better understood. *Magnesium ammonium phosphate (struvite) stones* almost always occur in persons with a persistently alkaline urine due to UTIs. In particular, the urea-splitting bacteria, such as *Proteus vulgaris* and the staphylococci, predispose the person to urolithiasis. Moreover, bacteria may serve as particulate nidi for the formation of any kind of stone. In avitaminosis A, desquamated cells from the metaplastic epithelium of the collecting system act as nidi.

Gout and diseases involving rapid cell turnover, such as the leukemias, lead to high uric acid levels in the urine and the possibility of *uric acid stones*. About half of the individuals with uric acid stones, however, have neither hyperuricemia nor increased urine urate but an unexplained tendency to excrete a persistently acid urine (under pH 5.5). This low pH favors uric acid stone formation—in contrast to the high pH that favors formation of stones containing calcium phosphate. *Cystine stones* are almost invariably associated with a genetically determined defect in the renal transport of certain **amino acids**, including cystine. In contrast to magnesium ammonium phosphate stones, both uric acid and cystine stones are more likely to form when the urine is relatively acidic.

Urolithiasis may also result from the lack of substances that normally inhibit mineral precipitation. Inhibitors of crystal formation in urine include Tamm-Horsfall pro-teín, osteopontin, pyrophosphate, mucopolysaccharides, diphosphonates, and a glycoprotein called nephrocalcin, but no deficiency of any of these substances has been consistently demonstrated in individuals with urolithiasis.

### Morphology

Stones are unilateral in about 80% of patients. Common sites of formation are renal pelvises and calyces and the bladder. Often, many stones are found in one kidney. They tend to be small (average diameter 2-3 mm) and may be smooth or jagged. Occasionally, progressive accretion of salts leads to the development of branching structures known as **staghorn calculi**, which create a cast of the renal pelvis and calyceal system. These massive stones are usually composed of magnesium ammonium phosphate.

### Clinical Course

Stones may be present without producing either symptoms or significant renal damage. This is particularly true with large stones lodged in the renal pelvis. Smaller stones may pass into the ureter, producing a typical intense pain known as *renal or ureteral colic*, characterized by paroxysms of flank pain radiating toward the groin. Often at this time there is *gross hematuria*. The clinical significance of stones lies in their capacity to obstruct urine flow or to produce sufficient trauma to cause ulceration and bleeding. In either case, they *predispose the sufferer to bacterial infection*. Fortunately, in most cases the diagnosis is readily made radiologically.

### Hydronephrosis

Hydronephrosis refers to dilation of the renal pelvis and calyces, with accompanying atrophy of the parenchyma, caused by obstruction to the outflow of urine. The obstruction may be sudden or insidious, and it may occur at any level of the urinary tract, from the urethra to the renal pelvis. The most common causes are as follows:

**Congenital:** Atresia of the urethra, valve formations in either ureter or urethra, aberrant renal artery compressing the ureter, renal ptosis with torsion, or kinking of the ureter  
**Acquired:**

Foreign bodies: Calculi, necrotic papillae  
Tumors: Benign prostatic hyperplasia, carcinoma of the prostate, bladder tumors (papilloma and carcinoma), contiguous malignant disease (retroperitoneal lymphoma, carcinoma of the

contiguous malignant disease (retroperitoneal lymphoma, carcinoma of the cervix or uterus) Inflammation: Prostatitis, ureteritis, urethritis, retroperitoneal fibrosis Neurogenic: Spinal cord damage with paralysis of the bladder Normal pregnancy: Mild and reversible

Bilateral hydronephrosis occurs only when the obstruction is below the level of the ureters. If blockage is at the ureters or above, the lesion is unilateral. Sometimes obstruction is complete, allowing no urine to pass; usually it is only partial.

### Pathogenesis

Even with complete obstruction, glomerular filtration persists for some time, and the filtrate subsequently diffuses back into the renal interstitium and perirenal spaces, whence it ultimately returns to the lymphatic and venous systems. Because of the continued filtration, the *affected calyces and pelvis become dilated*, often markedly so. The unusually high pressure thus generated in the renal pelvis, as well as that transmitted back through the collecting ducts, causes compression of the renal vasculature. Both arterial insufficiency and venous stasis result, although the latter is probably more important. The most severe effects are seen in the papillae, because they are subjected to the greatest increases in pressure. Accordingly, *the initial functional disturbances are largely tubular, manifested primarily by impaired concentrating ability*. Only later does glomerular filtration begin to diminish. Experimental studies indicate that serious irreversible damage occurs in about 3 weeks with complete obstruction, and in 3 months with incomplete obstruction. However, functional impairment can be demonstrated only a few hours after ureteral ligation. The obstruction also triggers an interstitial inflammatory reaction, leading eventually to interstitial fibrosis.

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### Morphology

**Bilateral** hydronephrosis (as well as unilateral hydronephrosis when the other kidney is already damaged or absent) leads to renal failure, and the onset of uremia tends to abort the natural course of the lesion. In contrast, **unilateral** involvements display the full range of morphologic changes, which vary with the degree and speed of obstruction. With subtotal or intermittent obstruction, the kidney may be massively enlarged (lengths in the range of 20 cm), and the organ may consist almost entirely of the greatly distended pelvicalyceal system. The renal parenchyma itself is compressed and atrophied, with obliteration of the papillae and flattening of the pyramids (Fig. 14-22). On the other hand, **when obstruction is sudden and complete, glomerular filtration is compromised relatively early, and as a consequence, renal function may cease while dilation is still comparatively slight**. Depending on the level of the obstruction, one or both ureters may also be dilated (**hydroureter**).

Microscopically the early lesions show tubular dilation, followed by atrophy and fibrous replacement of the tubular epithelium with relative sparing of the glomeruli. Eventually, in severe cases the glomeruli also become atrophic and disappear, converting the entire kidney into a thin shell of fibrous tissue. With sudden and complete obstruction, there may be coagulative necrosis of the renal papillae, similar to the changes of papillary necrosis. In uncomplicated cases the accompanying inflammatory reaction is minimal. Complicating pyelonephritis, however, is common.

### Clinical Course





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Figure 14-22 Hydronephrosis of the kidney, with marked dilation of the pelvis and calyces and thinning of renal parenchyma.

*Bilateral* complete obstruction produces anuria, which is soon brought to medical attention. When the obstruction is below the bladder, the dominant symptoms are those of bladder distention. Paradoxically, incomplete bilateral obstruction causes polyuria rather than oliguria, as a result of defects in tubular concentrating mechanisms, and this may obscure the true nature of the disturbance. Unfortunately, *unilateral* hydronephrosis may remain completely silent for long periods unless the other kidney is for some reason not functioning. Often the

shunt for long periods unless the other kidney is for some reason not functioning. Often the enlarged kidney is discovered on routine physical examination. Sometimes the basic cause of the hydronephrosis, such as renal calculi or an obstructing tumor, produces symptoms that indirectly draw attention to the hydronephrosis. Removal of obstruction within a few weeks usually permits full return of function; however, with time the changes become irreversible.





## TUMORS

Many types of benign and malignant tumors occur in the urinary tract. In general, benign tumors such as adenomas or medullary fibromas (interstitial cell tumors) have no clinical significance. The most common renal cell carcinoma, followed in frequency by nephroblastoma (Wilms tumor) and by primary tumors of renal cancer are rare and need not be discussed here. *Tumors of the lower urinary tract are also carcinomas.* They are described at the end of this section.

### Renal Cell Carcinoma

These tumors are derived from the renal tubular epithelium, and hence they are located predominantly in the cortex. They represent 80% to 85% of all primary malignant tumors of the kidney, and 2% to 3% of all cancers. There are about 30,000 cases per year; 40% of patients die of the disease. Carcinomas of the kidney are most common in men and men are affected about twice as commonly as women. The risk of developing these tumors is increased in obese patients, and those who have had occupational exposure to cadmium. Smokers who are elderly have a high incidence of renal cell carcinomas. The risk of developing renal cell cancer is increased 30-fold in patients with polycystic disease as a complication of chronic dialysis. The role of genetic factors in the causation of renal cell carcinoma is still unclear.

Renal cell cancers were formerly classified on the basis of morphology and growth patterns. However, a better understanding of the genetic basis of renal carcinomas have led to a new classification based on molecular biology. The three most common forms are as follows:

#### ***Clear Cell Carcinomas***

These are the most common type, accounting for 70% to 80% of renal cell cancers. Histologically they show a granular cytoplasm. Whereas the majority of them are sporadic, they also occur in familial forms called von Hippel-Lindau (VHL) disease. It is the study of VHL disease that has provided molecular insights into the causation of renal cell carcinoma. VHL disease is autosomal dominant and is characterized by predisposition to a variety of neoplasms, but particularly hemangioblastomas of the cerebellum and retina. Hundreds of bilateral renal cysts and bilateral, often multiple, clear cell carcinomas are found in these individuals. Those with VHL syndrome inherit a germ-line mutation of the *VHL* gene on chromosome 3. In sporadic cases, a somatic mutation of the *VHL* gene is found. Thus, the loss of both copies of this tumor suppressor gene gives rise to clear cell carcinoma. The *VHL* gene is involved in the majority of sporadic clear cell carcinomas. Cytogenetic abnormalities giving rise to changes in chromosome 3p26 are often seen in sporadic renal cell cancers. This region harbors the *VHL* gene (3p25.3). The *VHL* gene is inactivated by a somatic mutation or hypermethylation in 60% of sporadic cases. Thus, homozygous deletion of the *VHL* gene is a common underlying molecular abnormality in both sporadic and familial forms of clear cell carcinoma. The *VHL* gene is thought to be limiting the angiogenic response to hypoxia; thus, its absence may lead to increased angiogenesis. An uncommon familial form of clear cell carcinoma unrelated to VHL disease also involves cytogenetic changes on chromosome 3p.

#### ***Papillary Renal Cell Carcinomas***

These comprise 10% to 15% of all renal cancers. As the name indicates, they show a papillary growth pattern. They are multifocal and bilateral and appear as early-stage tumors. Like clear cell carcinomas they occur in sporadic and familial forms. In these tumors, papillary renal cancers have no abnormality of chromosome 3. The culprit in the causation of papillary renal cancer is the *MET* proto-oncogene, located on chromosome 7q31. The *MET* gene is a tyrosine kinase receptor for the growth factor. It is an increased gene dosage of the *MET* gene due to duplications of chromosome 7 that is found in the proximal tubular epithelial cell precursors of papillary carcinomas. In keeping with this, trisomy of chromosome 7 is found in the familial cases. In these individuals, along with increased gene dosage there are activating mutations of the *MET* gene. In sporadic cases there is duplication or trisomy of chromosome 7 but there is no mutation of the *MET* gene. A translocation, involving chromosome 8q24 close to the *c-MYC* gene, is also associated with some cases of papillary renal cancer.

#### ***Chromophobe Renal Carcinomas***

These are the least common, representing 5% of all renal cell carcinomas. They arise from interstitial cells of the kidney.

These are the least common, representing 3% of all renal cell carcinomas. They arise from intercalated ducts. The name denotes the observation that the tumor cells stain more darkly (i.e., they are less clear) than other renal cell tumors. They are unique in having multiple losses of entire chromosomes, including chromosomes 1, 2, 3, 6, 10, 13, 17, and 22, resulting in extreme hypodiploidy. Because of multiple losses, the "critical hit" has not been determined. In general, they have a good prognosis.

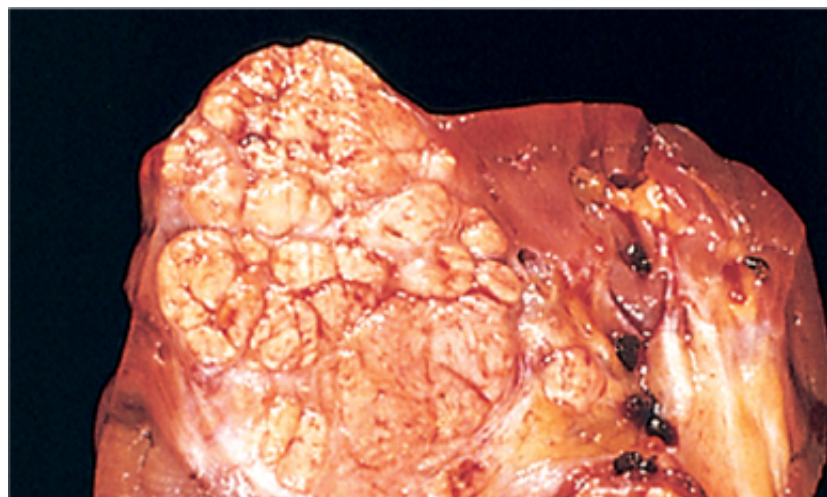
### **Morphology**

**Clear cell cancers** (the most common form) are usually solitary and large when symptomatic (masses 3-15 cm in diameter), but increased use of high-resolution radiographic techniques for diagnosis of unrelated problems has led to the detection of even smaller lesions. They may arise from the renal cortex. The cut surface of clear cell renal cell carcinomas is **yellow to orange to gray** with **prominent areas of cystic softening or of hemorrhage**, either fresh or old (Fig. 1). The tumor margins are well defined. However, at times small processes project into the surrounding normal renal parenchyma. Small satellite nodules are found in the surrounding substance, providing clear evidence of the aggressiveness of these lesions. As the tumor enlarges, it may fungate through the renal capsule, extending through the calyces and pelvis as far as the ureter. Even more frequently, it **invades the renal vein** and grows as a solid column within this vessel, sometimes extending in this fashion as far as the inferior vena cava and even into the right side of the heart. Occasionally, it invades into the perinephric fat and adrenal gland.

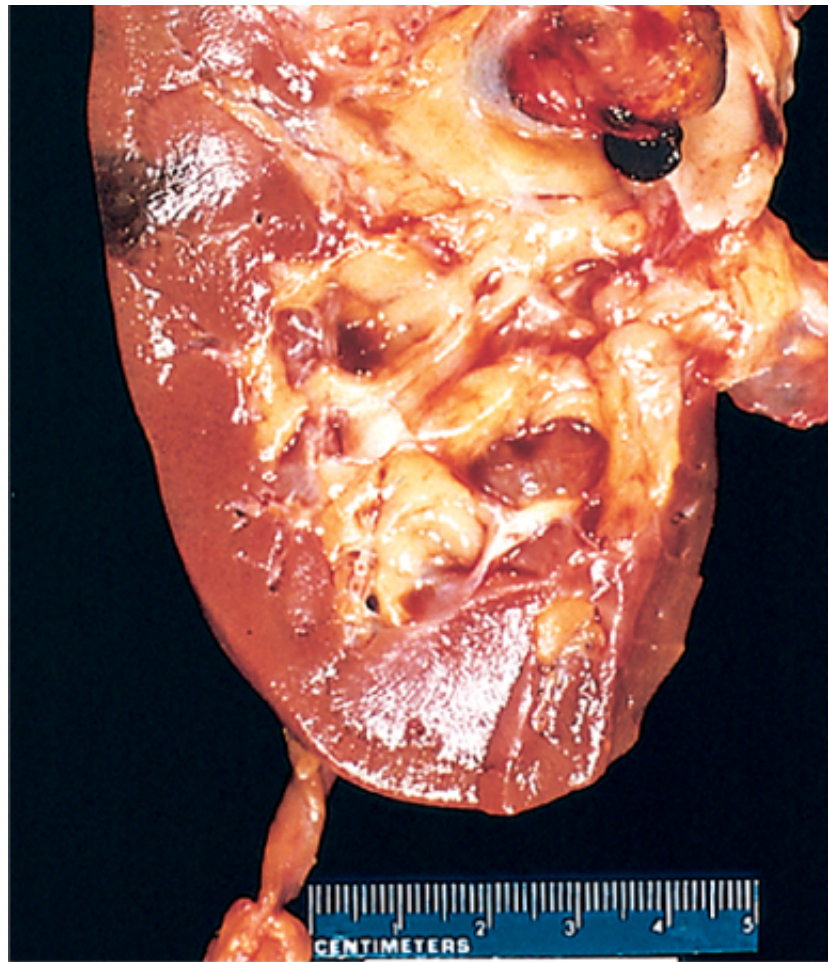
Depending on the amounts of lipid and glycogen present, **the tumor cells of clear cell carcinoma may appear almost vacuolated or may be solid**. The classic vacuolated cells are demarcated only by their cell membranes. The nuclei are usually small and uniform. At the other extreme are granular cells, resembling the tubular epithelium, which have nuclei enclosed within granular pink cytoplasm. Some tumors exhibit marked degrees of pleomorphism, with numerous mitotic figures and markedly enlarged, hyperchromatic, pleomorphic nuclei. In some cases, a mixture of clear cells and solid, granular cells, all intergradations may be found. The cellular arrangement is widely variable. The cells may form abortive tubules or may cluster in cords or disorganized sheets. The stroma is usually scant but highly vascularized.

**Papillary renal cell carcinomas** exhibit varying degrees of papilla formation with 1-3 papillae. They tend to be bilateral and multiple. They may also show gross evidence of necrosis, hemorrhage, and degeneration, but they are less vibrantly orange-yellow because of their lower lipid content. They have clear or, more commonly, pink cytoplasm. **Chromophobe-type renal cell carcinoma** has a grossly tan-brown color. The cells usually have clear, flocculent cytoplasm with very prominent cell membranes. The nuclei are surrounded by halos of cleared cytoplasm. Ultrastructurally, characteristic macrovesicles are seen.

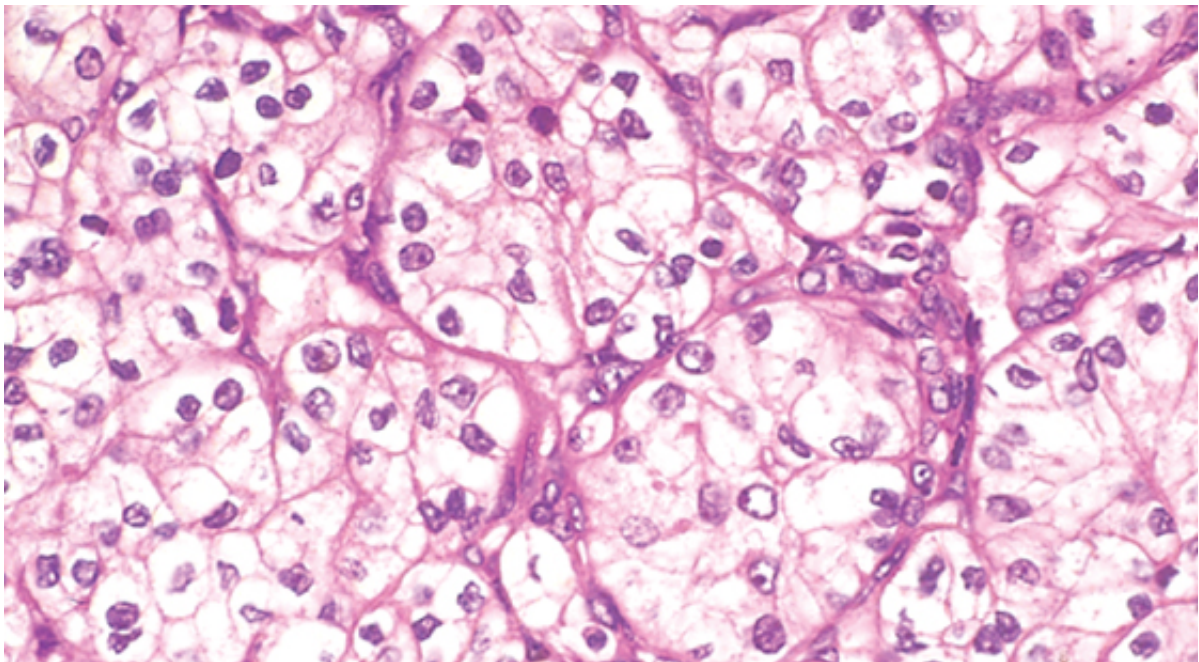
### *Clinical Course*

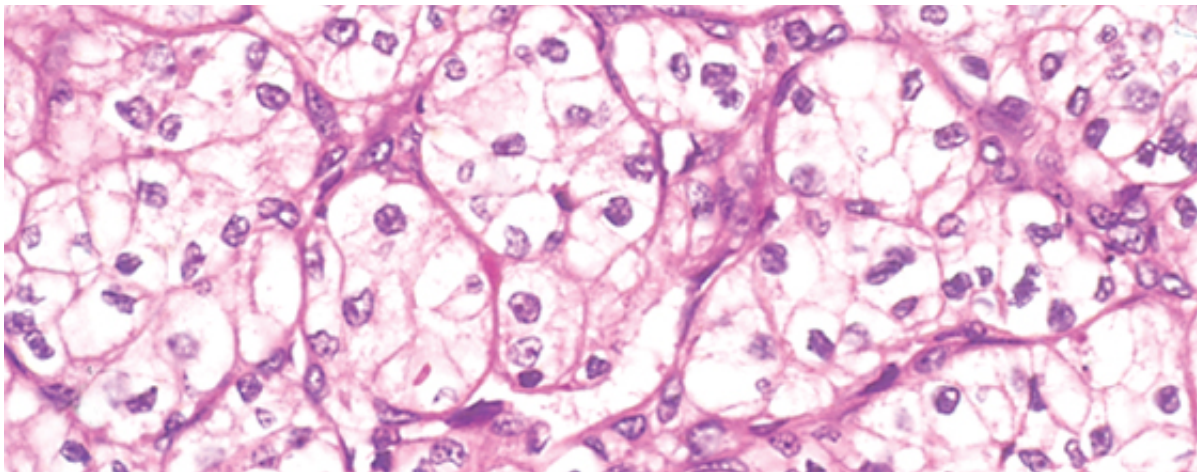






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Figure 14-23 Renal cell carcinoma: typical cross-section of yellowish, spherical neoplasm in one pole of the kidney vein.





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Figure 14-24 High-power detail of the clear cell pattern of renal cell carcinoma.

Renal cell carcinomas have several peculiar clinical characteristics that create especially difficult diagnosis. Symptoms vary, but the *most frequent presenting manifestation is hematuria, occurring in more than 80% of cases*. It tends to be intermittent and fleeting, superimposed on a steady microscopic hematuria. Less common (studies for unrelated conditions), the tumor may declare itself simply by virtue of its size, when it is large enough to cause pain and a *palpable mass*. Extra-renal effects are *fever* and *polycythemia*, both of which may be associated with the tumor, which, because they are nonspecific, may be misinterpreted for some time before their true significance is appreciated. The tumor produces a variety of hormone-like substances, resulting in hypercalcemia, hypertension, Cushing syndrome, and masculinization. These, as will be recalled from [Chapter 6](#), are *paraneoplastic syndromes*. In many cases, the tumor is silent and is discovered only after its metastases have produced symptoms. The prevalent location of metastases is in the bones. It must be apparent that renal cell carcinoma presents in many fashions, some quite deviant from the norm. *palpable abdominal mass, and dull flank pain is characteristic.*

### Wilms Tumor

Although Wilms tumor occurs infrequently in adults, it is the third most common organ cancer in children. It is therefore one of the major cancers of children. These tumors contain a variety of cell and tissue components, including epithelium, connective tissue, and mesoderm. Wilms tumor, like retinoblastoma, may arise sporadically or be familial, with the susceptibility being an autosomal dominant trait. This tumor is discussed in greater detail in [Chapter 7](#) along with other tumors of childhood.

### SUMMARY

#### Renal Cell Carcinoma

Renal cell carcinomas account for 2-3% of all cancers in adults; classified in three types. *Clear cell carcinomas* are the most common; associated with homozygous deletion of the *VHL* tumor suppressor protein; tumors frequently invade the renal vein. *Papillary carcinomas* are frequently associated with increased expression and amplification of the *RET* oncogene; tend to be bilateral and multiple, and show varying degrees of anaplasia. *Chromophobe renal cell carcinomas* are less common; tumors are usually small and well circumscribed.

### Tumors of the Urinary Bladder and Collecting System (Renal Calyces, Renal Pelvis, Ureter,

The entire urinary collecting system from renal pelvis to urethra is lined with transitional epithelium. Tumors in the collecting system above the bladder are relatively uncommon. Bladder cancer is the most frequent cause of death than are kidney tumors. Nevertheless, in the individual case a small tumor may cause urinary outflow obstruction and have greater clinical significance than a much larger mass. Consider first the range of histologic patterns as they occur in the urinary bladder and then their clinical significance.



consider first the range of histologic patterns as they occur in the urinary bladder and then their clinical

### Morphology

Tumors arising in the urinary bladder range from small benign papillomas to large invasive carcinomas (Fig. 14-25). These tumors are classified into a rare benign papilloma, a group of papillary tumors with malignant potential, and two grades of urothelial carcinoma (low and high grade).

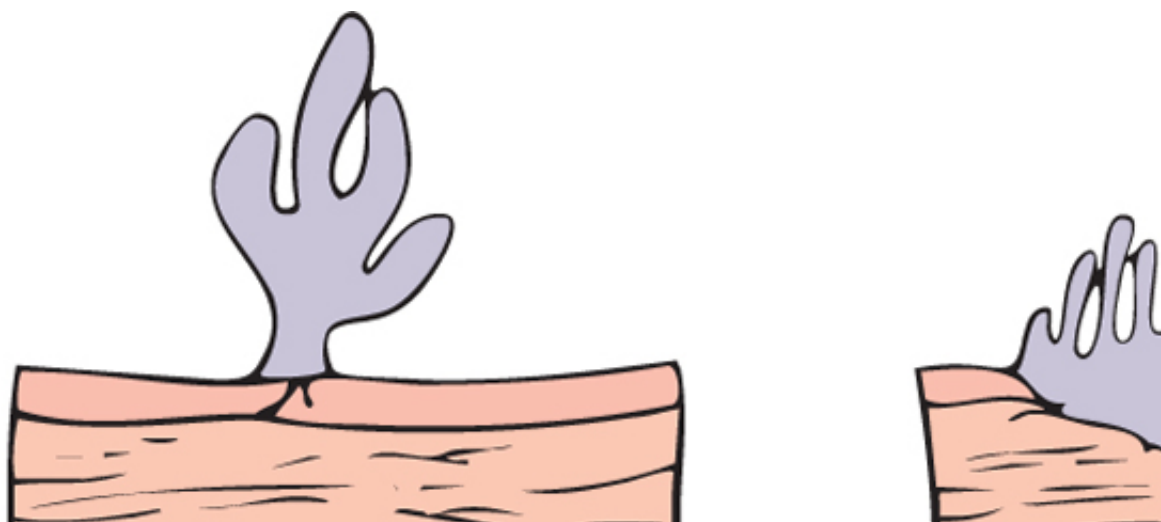
The very rare benign **papillomas** are 0.2- to 1.0-cm frondlike structures having a dome-shaped surface covered by multilayered, well-differentiated transitional epithelium. In some of these tumors, the epithelium appears as normal as the mucosal surface from whence the tumors arise. They are usually solitary. They are almost invariably noninvasive and benign, and they rarely recur.

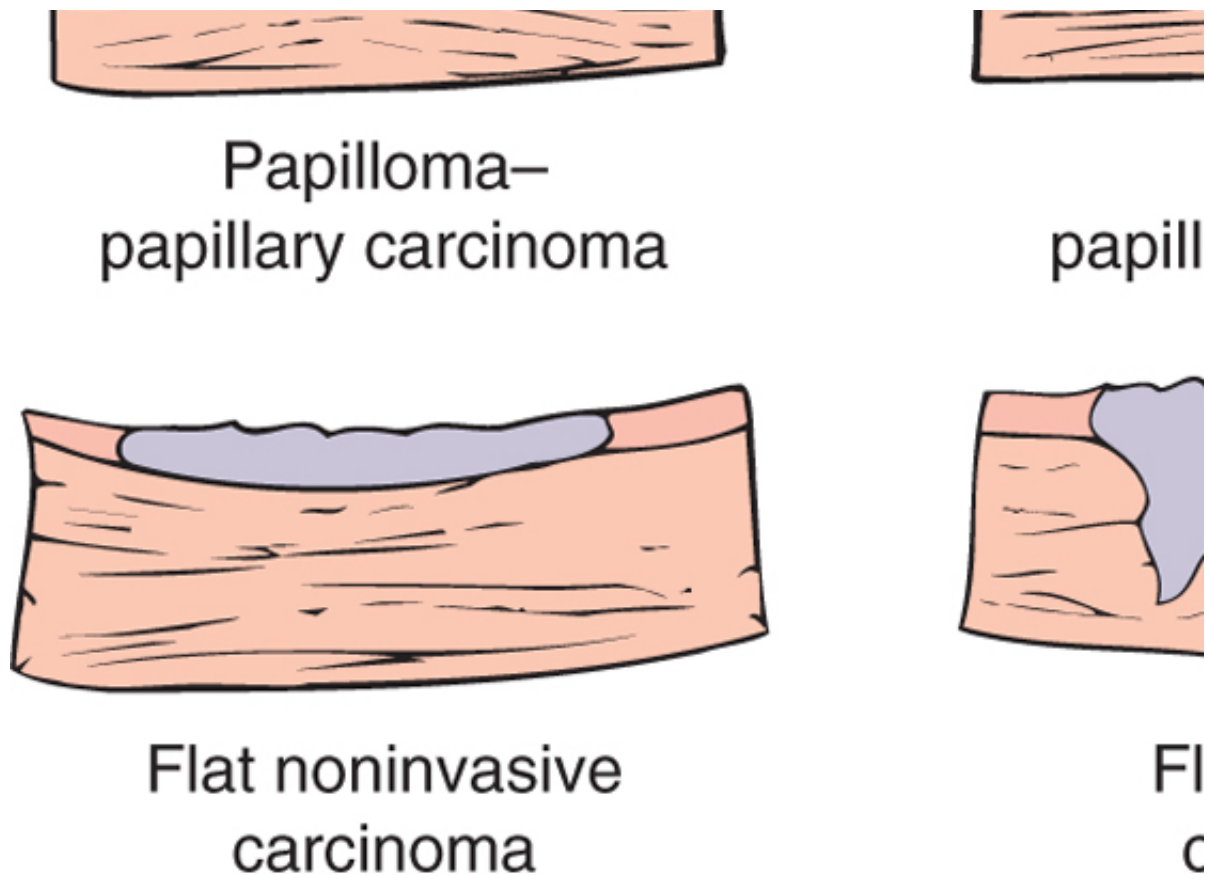
**Urothelial (transitional) cell carcinomas** range from papillary to flat, noninvasive to high grade. Low-grade carcinomas (Fig. 14-26) are always papillary and are rarely invasive. They recur after removal. Whether the regrowth is a true recurrence or a second primary tumor is uncertain. Increasing degrees of cellular atypia and anaplasia are encountered in papillary exophytic tumors, but they are accompanied by an increase in the size of the lesion and evidence of invasion of the underlying muscular layers. High-grade cancers can be papillary or occasionally flat; they may have a shaggy necrotic surface, invade deeper, and have a shaggier necrotic surface than do low-grade tumors. Occasionally, these cancers show foci of squamous cell differentiation, but only 5% are true **squamous cell carcinomas**. Carcinomas of grades II and III infiltrate surrounding tissues, regional nodes, and, on occasion, metastasize widely.

In addition to overt carcinoma, an **in situ stage of bladder carcinoma** can be recognized in individuals with previous or simultaneous papillary or invasive tumors. Indeed, widespread hyperplasia and dysplasia may be present. It is now thought that these epithelial changes are caused by the generalized influence of a putative carcinogen on urothelium and are precursors of invasive carcinomas in some persons. However, despite the presence of these epithelial lesions, the bladder tumors, even when multiple, are monoclonal in origin. The descendants of a single transformed cell can seed multiple areas of the mucosa.

### Clinical Course

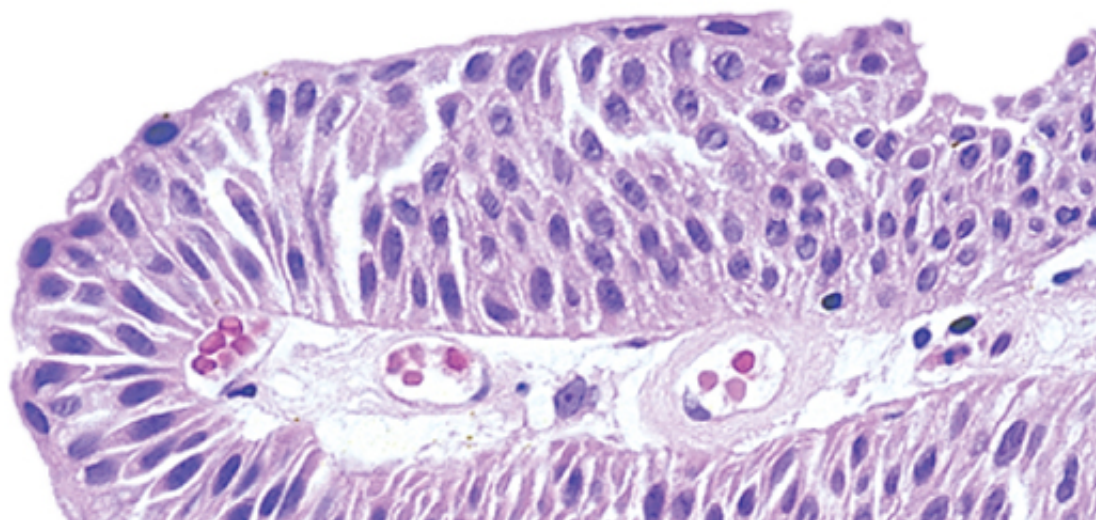
*Painless hematuria is the dominant clinical presentation* of all these tumors. Because most arise in the bladder, they affect men about three times as frequently as women and usually develop between the ages of 50 and 70. In persons with no known history of exposure to industrial solvents, bladder tumors are 50 times more common than in persons exposed to naphthylamine. Cigarette smoking, chronic cystitis, schistosomiasis of the bladder, and certain drugs are believed to induce higher rates of this cancer. A wide variety of genetic abnormalities are seen in bladder tumors. Abnormalities involving several genes on chromosome 9 (including p16), p53, and FGFR3 are the most common.



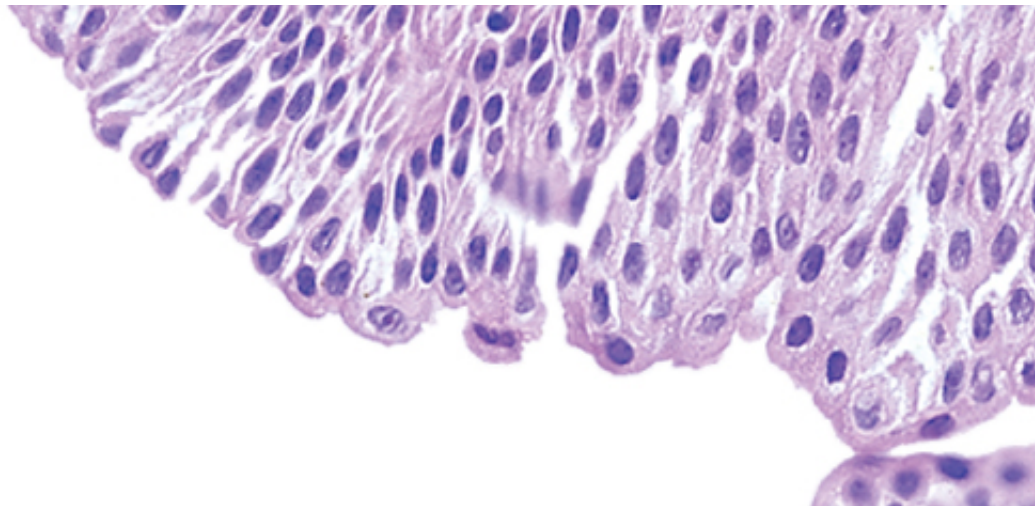


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Figure 14-25 Four morphologic patterns of bladder tumor.

*The clinical significance of bladder tumors depends on their histologic grade and differentiation and on the depth of invasion of the lesion.* Except for the clearly benign papillomas, all tend stubbornly to recur after resection. If the tumor or urethral orifices cause urinary tract obstruction. In general, with low-grade shallow lesions, the prognosis is better. If deep penetration of the bladder wall has occurred, the 5-year survival rate is less than 20%. Over







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 Figure 14-26 Low-grade papillary urothelial carcinoma of the bladder. The delicate papilla is covered

Although papillary and cancerous neoplasms of the lining epithelium of the collecting system occur more often in the bladder, they nonetheless make up 5% to 10% of primary renal tumors. Painless hematuria is a common feature of these lesions, but in their critical location they produce pain in the costovertebral angle as hydronephrosis develops. Obstruction of the pelvis, calyces, and renal vein worsens the prognosis. Despite removal of the tumor by nephroureterectomy, only 10% to 20% survive for 5 years. Cancer of the ureter is fortunately the rarest of the tumors of the collecting system, accounting for only 10%.

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## 15 The Oral Cavity and the Gastrointestinal Tract\*

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### ORAL CAVITY

Diseases of the oral cavity can be broadly divided into two groups: those affecting the soft tissues (including the salivary glands) and those that involve the teeth. Only the more common conditions affecting the soft tissues are considered in this chapter. Excluded are extra-oral diseases that sometimes involve the mouth and pharynx, such as diphtheria, lichen planus, and leukemia, as well as dental disorders.



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## ORAL CAVITY

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## ULCERATIVE AND INFLAMMATORY LESIONS

Although several ulcerative and inflammatory conditions are discussed here, it is important to remember that cancer may produce ulcerations in the oral cavity and must be considered in the differential diagnosis.

### Aphthous Ulcers (Canker Sores)

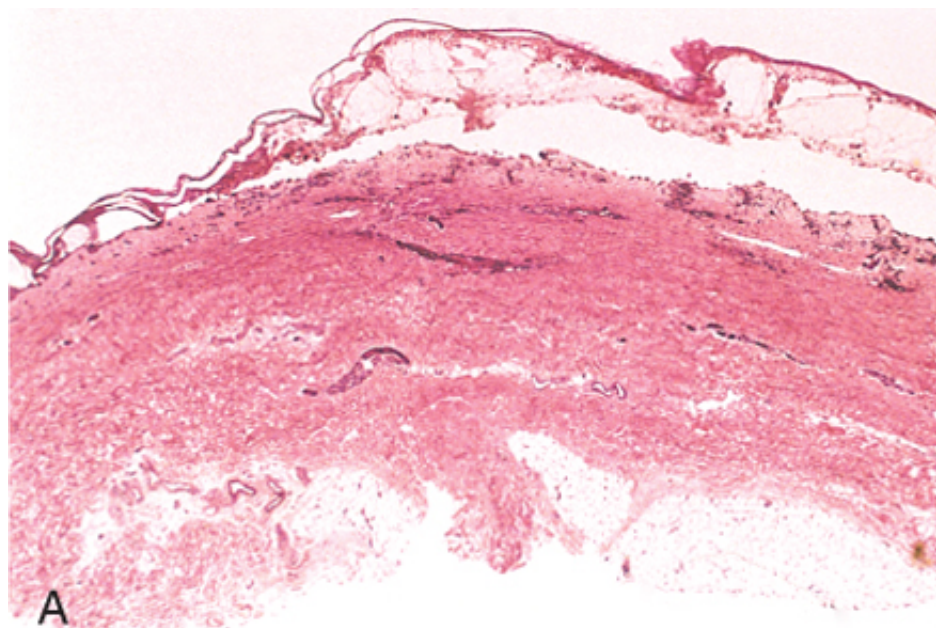
These lesions are extremely common, small (usually <5 mm in diameter), painful, shallow ulcers. They are rounded, superficial erosions, often covered with a gray-white exudate and having an erythematous border. They occur in groups on the nonkeratinized oral mucosa, particularly the soft palate, buccolabial mucosa, floor of the mouth, and tongue. They are more common in the first 2 decades of life and are often triggered by stress, fever, or activation of inflammatory bowel disease. In patients who are not immunosuppressed or do not have recurrent herpesvirus, an autoimmune basis is suspected. The canker sores are self-limited and usually resolve within 1–2 weeks. They recur in the same or a different location in the oral cavity.

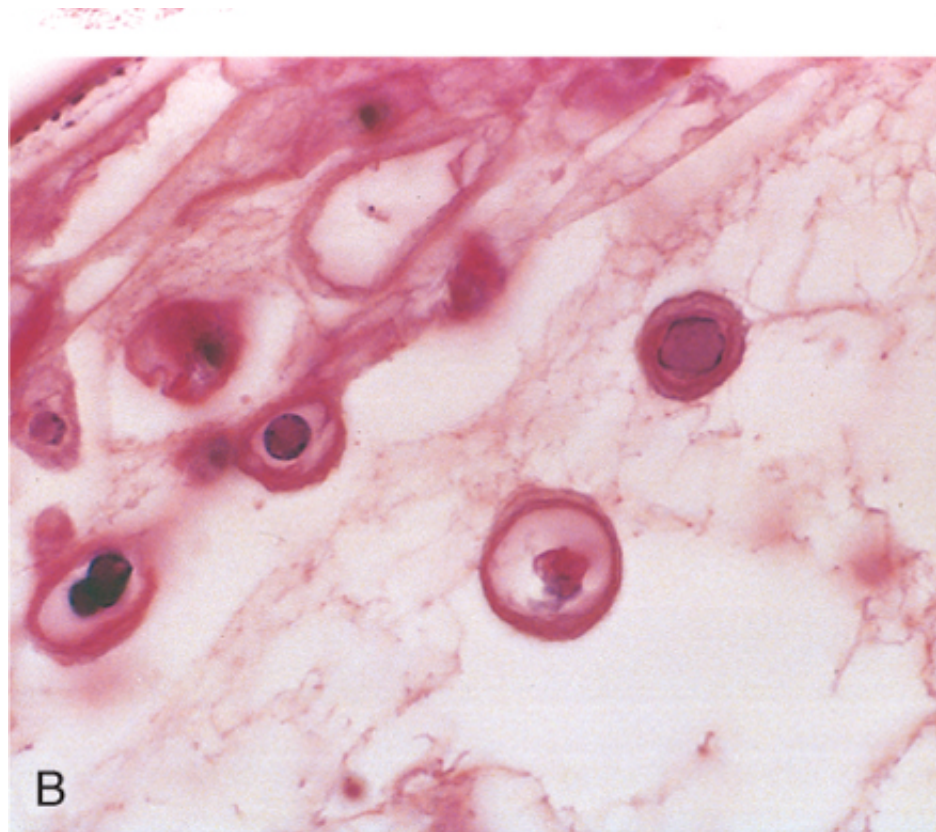
### Herpesvirus Infection

*Herpetic stomatitis is an extremely common infection caused by herpes simplex virus (HSV) type 1. It is transmitted from person to person, most often by kissing; by middle life over three-fourths of the population have been infected. The infection is asymptomatic, but the virus persists in a dormant state within ganglia about the mouth. Upon reactivation of the virus (which may be caused by fever, sun or cold exposure, respiratory tract infection, or stress), small (<5 mm in diameter) vesicles containing clear fluid appear. They occur most often on the lips or around the mouth as cold sores or fever blisters. They soon rupture, leaving shallow, painful ulcers that heal within a few days. This is a common condition.*

#### Morphology

The vesicles begin as an intraepithelial focus of intercellular and intracellular edema. The cells become ballooned and develop **intranuclear acidophilic viral inclusions**. Sometimes the infected cells form giant cells known as **multinucleated polykaryons**. Necrosis of the infected cells and collections of edema fluid account for the intraepithelial vesicles detected clinically. The presence of the inclusion-bearing cells or polykaryons in smears of blister fluid constitutes the definitive diagnosis for HSV infection.





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 Figure 15-1 Herpesvirus pharyngitis. **A**, Herpesvirus blister in mucosa. **B**, High-power view of cells from blister in inclusion bodies.

Antiviral agents may accelerate healing of the lesions. In 10% to 20% of those with this condition, a more virulent disseminated eruption develops, producing multiple vesicles throughout the oral cavity (*herpetic gingivostomatitis*), and lymphadenopathy. In particularly severe cases, viremia may occur and produce disseminated visceral lesions. HSV type 1 may localize in many other sites, including the esophagus when a nasogastric tube is introduced through an infected oral cavity. As a result, the herpes produced by HSV type 2 (the agent of *herpes genitalis*) is increasingly seen in the oral cavity, which have the same histologic characteristics as those that develop on the genital mucosa.

### Oral Candidiasis

*Candida albicans* is a normal inhabitant of the oral cavity found in 30% to 40% of the population; impairment of the usual protective mechanisms. *Pseudomembranous candidiasis* (*thrush*, *monilia*) of the oral cavity and is particularly common among persons rendered vulnerable by diabetes mellitus, therapy, immunodeficiency, or debilitating illnesses such as disseminated cancer. Persons with the (AIDS) are at particular risk.

#### Morphology

Typically, **oral candidiasis takes the form of an adherent white, curdlike, circumscribed plaque anywhere within the oral cavity (Fig. 15-2)**. The pseudomembrane can be scraped off, revealing an underlying granular erythematous inflammatory base. Histologically, the pseudomembrane consists of a myriad of fungal organisms superficially attached to the underlying mucosa. In mild cases, there is minimal ulceration, but in severe cases the entire mucosa may be denuded. The fungus is seen as these pseudomembranes as boxcar-like chains of tubular cells producing pseudohyphae and ovoid yeast forms, typically 2 to 4  $\mu$ m in greatest diameter.

In the particularly vulnerable host, candidiasis may spread into the esophagus, especially when a it may produce wides-pread visceral lesions when the fungus gains entry into the bloodstream. Di threatening infection that must be treated aggressively. For poorly understood reasons, local canc not only in predisposed females but also in apparently healthy young women, particularly during p oral contraceptives or broad-spectrum antibiotics.

### **AIDS and Kaposi Sarcoma**



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Figure 15-2 Oral candidiasis ("thrush"). A white plaquelike membrane coats the gingival mucosa of the left lower jaw of candidal pseudohyphae. (Courtesy of Dr. Harvey P. Kessler, Department of Oral Surgery, College of Dentist

AIDS and less advanced forms of human immune deficiency virus (HIV) infection are often associ

may take the form of candidiasis, herpetic vesicles, or some other microbial infection (producing an uncommon lesion seen virtually only in persons infected with HIV. It consists of white confluent patches that have a "hairy" or corrugated surface resulting from marked epithelial thickening. It is caused by HPV cells. Occasionally, the development of hairy leukoplakia calls attention to the existence of the underlying HIV infection.

More than 50% of individuals with *Kaposi sarcoma* (see [Chapter 10](#)) develop intraoral purpuric discolorations; sometimes this involvement constitutes the presenting manifestation.



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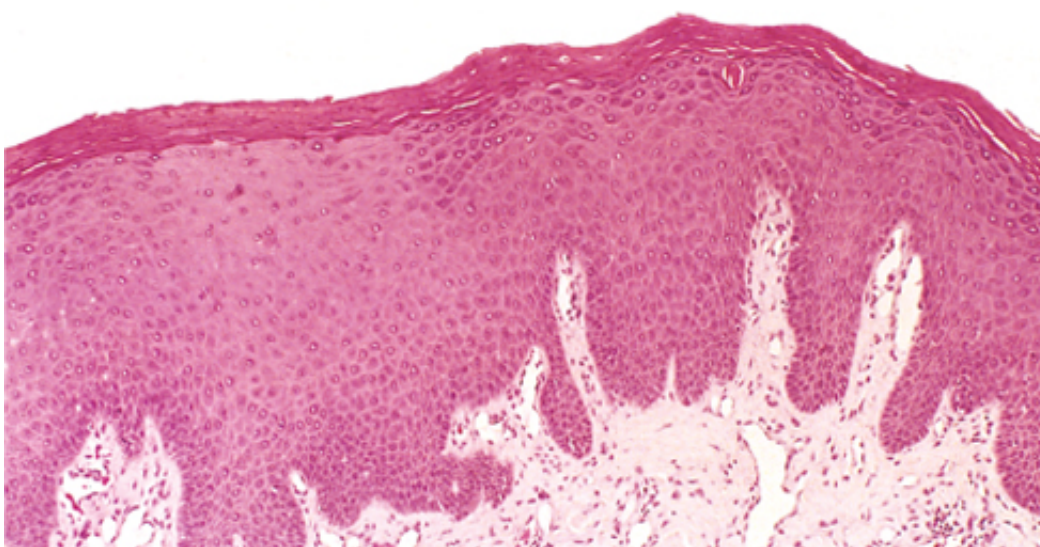


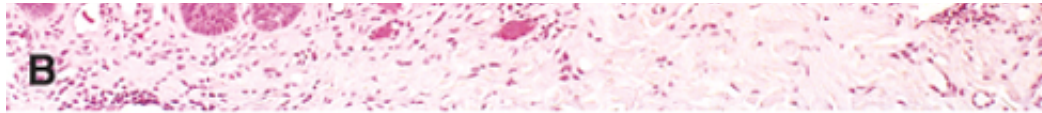


## LEUKOPLAKIA AND ERYTHROPLAKIA

As generally used, the term *leukoplakia* refers to a *whitish, well-defined mucosal patch or plaque caused by epidermal thickening or hyperkeratosis*. As defined by the World Health Organization, leukoplakia is a white patch or plaque that can not be scraped off and cannot be characterized as any other disease. Thus, the term is not applied to other white lesions, such as those caused by candidiasis, lichen planus, or many other disorders.

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Figure 15-3 **A**, Leukoplakia of the tongue in a smoker. Microscopically, this lesion showed severe dysplasia with transformation to squamous cell carcinoma in the posterior elevated portion (*arrow*). **B**, Leukoplakia with marked epithelial thickening and hyperkeratosis.

The plaques are more frequent among older men and are most often on the vermillion border of the lower lip, buccal mucosa, the hard and soft palates, and less frequently on the floor of the mouth and other intraoral sites. They appear as localized, sometimes multifocal or even diffuse, smooth or roughened, leathery, white, discrete areas of mucosal thickening. On microscopic evaluation they vary from banal hyperkeratosis without underlying epithelial dysplasia to mild to severe dysplasia bordering on carcinoma in situ (Fig. 15-3). Only histologic evaluation distinguishes these lesions. The lesions are of unknown cause except that there is a *strong association with the use of tobacco*, particularly pipe smoking and smokeless tobacco (pouches, snuff, chewing). Less strongly implicated are *chronic friction*, as from ill-fitting dentures or jagged teeth; *alcohol abuse*; and irritant foods. More recently, human papillomavirus antigen has been identified in some tobacco-related lesions, raising the possibility that the virus and tobacco act in concert in the induction of these lesions.

Oral leukoplakia is an important finding because 3% to 25% (depending somewhat on location) undergo transformation to squamous cell carcinoma (see Fig. 15-3A). It is impossible to distinguish the innocent lesion from the ominous one on visual inspection. The transformation rate is greatest with lip and tongue lesions and lowest with those on the floor of the mouth. Those lesions that display significant dysplasia on microscopic examination have a greater probability of cancerous transformation.

Three somewhat related lesions must be differentiated from the usual oral leukoplakia. Hairy leukoplakia, described earlier and seen virtually only in persons with AIDS, has a corrugated or "hairy" surface rather than the white, opaque thickening of oral leukoplakia and has not been related to the development of oral cancer. *Verrucous leukoplakia* shows a corrugated surface caused by excessive hyperkeratosis. This seemingly innocuous form of leukoplakia recurs and insidiously spreads over time, resulting in a diffuse warty-type of oral lesion that may yet harbor squamous cell carcinoma. *Erythroplakia* refers to red, velvety, often granular, circumscribed areas that may or may not be elevated, having poorly defined, irregular boundaries. Histologically, erythroplakia almost invariably reveals marked epithelial dysplasia (the malignant transformation rate is >50%), so recognition of this lesion becomes even more important than identification of oral leukoplakia.





## CANCERS OF THE ORAL CAVITY AND TONGUE

*The overwhelming preponderance of oral cavity cancers are squamous cell carcinomas.*

Although they represent only about 3% of all cancers in the United States, they are disproportionately important clinically. Almost all are readily accessible to biopsy and early identification, but about half result in death within 5 years and indeed may have already metastasized by the time the primary lesion is discovered. These cancers tend to occur late in life and rarely before the age of 40 years. The various influences thought to be important in development of these cancers are summarized in [Table 15-1](#).

### *Clinical Features*

These lesions may cause local pain or difficulty in chewing, but many are relatively asymptomatic and so the lesion (very familiar to the exploring tongue) is ignored. As a result, a significant number are not discovered until beyond cure. The overall 5-year survival rates after surgery and adjuvant radiation and chemotherapy are about 40% for cancers of the base of the tongue, pharynx, and floor of the mouth without lymph node metastasis, compared with less than 20% for those with lymph node metastasis. When these cancers are discovered at an early stage, 5-year survival can exceed 90%.

**Table 15-1. Risk Factors for Oral Cancer**

Factor	Comments
Leukoplakia, erythroplakia	Risk of transformation in leukoplakia 3% to 25% More than 50% risk in erythroplakia
Tobacco use	Best-established influence, particularly pipe smoking and smokeless tobacco
Human papillomavirus types 16 and 18	Identified by molecular probes in 30% to 50% of cases; probably have a role in a subset of cases
Alcohol abuse	Weaker influence than tobacco use, but the two habits interact to greatly increase risk
Protracted irritation	Weakly associated

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### **Morphology**

The three predominant sites of origin of oral cavity carcinomas are (in order of frequency) the (1) vermilion border of the lateral margins of the lower lip, (2) floor of the mouth, and (3) lateral borders of the mobile tongue. Early lesions appear as pearly white to gray, circumscribed thickenings of the mucosa closely resembling leukoplakic patches. They then may grow in an exophytic fashion to produce readily visible and palpable nodular and eventually fungating lesions, or they may assume an endophytic, invasive pattern with central necrosis to create a cancerous ulcer. The squamous cell carcinomas are usually moderately to well-differentiated keratinizing tumors ([Fig. 15-4](#)). Before the lesions become advanced it may be possible to identify epithelial atypia, dysplasia, or carcinoma in situ in the margins, suggesting origin from leukoplakia or erythroplakia. Spread to regional nodes is present at the time of initial diagnosis only rarely with lip cancer, in about 50% of cases of tongue cancer, and in more than 60% of those with cancer of the floor of the mouth. More remote spread to tissues or organs in the thorax or abdomen is less common than extensive regional spread.

## SUMMARY

**Diseases of the Oral Cavity** *Aphthous ulcers* are painful superficial ulcers of unknown etiology that are often triggered by stress. *Herpes simplex virus infection* causes a usually self-limited infection with vesicles (cold sores, fever blisters) that typically rupture and heal but may leave latent virus in nerve ganglia. Oral *Candida infection* is seen in immunosuppressed individuals and manifests as a plaque; fungal dissemination is a potentially serious outcome. *Leukoplakia* is a mucosal plaque caused by epidermal thickening; depending on the location 3% to 25% may progress to squamous cell carcinoma. The majority of oral cancers are *squamous cell carcinomas*.



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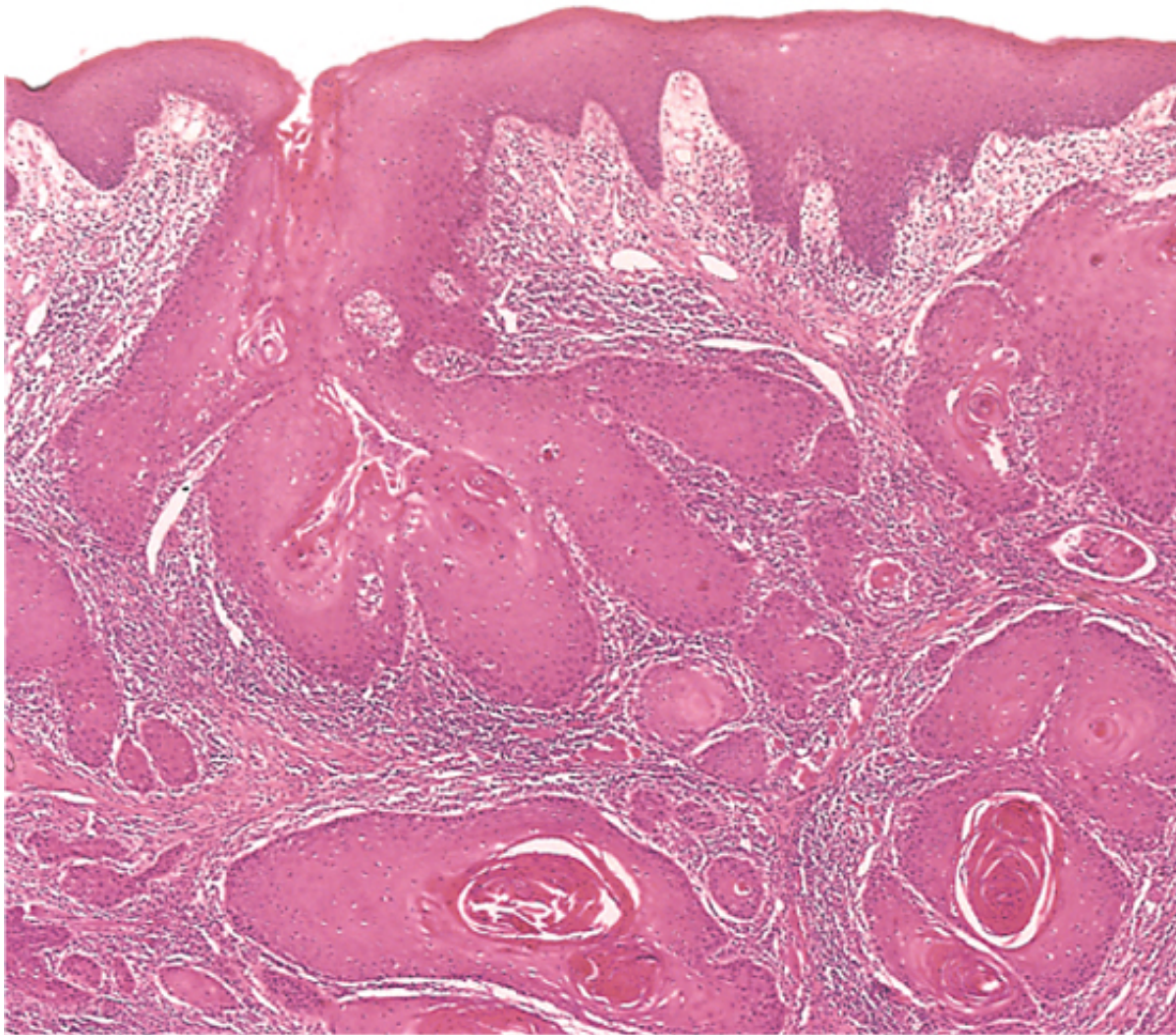




## SALIVARY GLAND DISEASES

Although diseases primary to the major salivary glands are in general uncommon, the parotids be Among the many possible disorders, attention is restricted here to sialadenitis and salivary gland i

### Sialadenitis



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Figure 15-4 Oral squamous cell carcinoma. Invasive tumor islands show formation

Inflammation of the major salivary glands may be of traumatic, viral, bacterial, or autoimmune origin. A cystic degeneration of the salivary glands is *mucocoele*, resulting from blockage or rupture of a salivary gland duct, with consequent accumulation of secretions in the surrounding tissues. Mucocoeles are most often found in the lower lip, as a consequence of trauma. A chronic inflammation of the salivary glands is *sialadenitis*, which may be of bacterial or viral origin. Sialadenitis is the infectious viral disease *mumps*, which may produce enlargement of all the major salivary glands. Although several viruses may cause mumps, the most important cause is a paramyxovirus, the mumps virus. It usually produces a diffuse, interstitial inflammation marked by edema and sometimes, by focal necrosis. Although childhood mumps is self-limited and rarely creates residual damage, it may be complicated by pancreatitis or orchitis; the latter sometimes causes permanent sterility.

*Bacterial sialadenitis* most often occurs secondary to ductal obstruction resulting from stone formation after retrograde entry of oral cavity bacteria under conditions of severe systemic dehydration such as common bacteria causing the infection are *Staphylococcus aureus* and *Streptococcus viridans*. Possible conditions, compromised immune function, or on medications contributing to oral or systemic dehydration bacterial sialadenitis. The sialadenitis may be largely interstitial, or it may cause focal areas of suppuration.

Chronic sialadenitis arises from decreased production of saliva with subsequent inflammation. This is seen in *sialadenitis*, which is almost invariably bilateral. This is seen in Sjögren syndrome, discussed in [C](#) (major and minor), as well as the lacrimal glands, may be affected in this disorder, which presents with dry eye (keratoconjunctivitis sicca). The combination of salivary and lacrimal gland inflammatory enlargement, xerostomia, whatever the cause, is sometimes referred to as *Mikulicz syndrome*. The causes include autoimmune and idiopathic lymphoepithelial hyperplasia.

## Salivary Gland Tumors

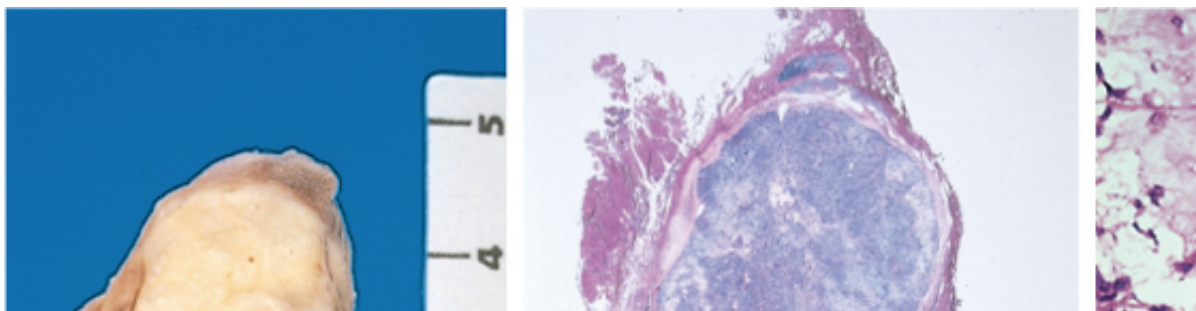
The salivary glands give rise to a diversity of tumors. About 80% of tumors occur within the parotid, submandibular glands. Males and females are affected about equally, usually in the sixth or seventh decade. About 80% of these tumors are benign, whereas in the submaxillary glands only half are benign. Thus, *if a tumor arises in the submaxillary glands is more ominous than one in the parotids*. The dominant tumor arising in the parotid is the *pleomorphic adenoma*, which is sometimes called a mixed tumor of salivary gland origin. Much less frequent is the *lymphomatosum* (Warthin tumor). Collectively, these two types account for three-fourths of parotid tumors. Clinically as a mass causing a swelling at the angle of the jaw. The most malignant tumor of the salivary glands is the *carcinoma*, which occurs mainly in the parotids. When primary or recurrent benign tumors are present, malignant transformation may occur, referred to then as a *malignant mixed* salivary gland tumor. Malignancy is more common (15%) than in the submandibular glands (40%). Only the benign pleomorphic adenoma and Warthin's tumor are described.

### *Pleomorphic Adenoma (Mixed Tumor of Salivary Glands)*

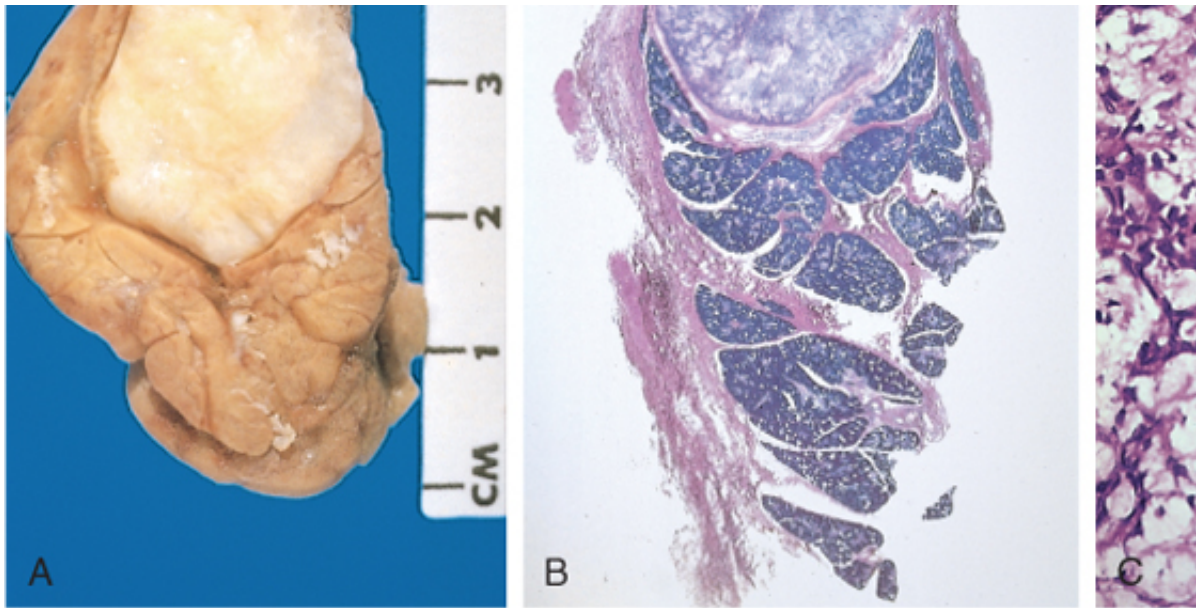
This tumor accounts for more than 90% of benign tumors of the salivary glands. It is a slow-growing, well-encapsulated lesion rarely exceeding 6 cm in greatest dimension. Most often arising in the superficial lobe of the parotid gland, it presents as a swelling at the angle of the jaw and can be readily palpated as a discrete mass. It is nonetheless brought to medical attention. Despite the tumor's encapsulation, histologic examination often reveals that it penetrates the capsule. Adequate margins of resection are thus necessary to prevent recurrences. The facial nerve, which courses through the parotid gland. On average, about 10% of excisions are followed by recurrence.

### Morphology

The characteristic histologic feature of pleomorphic adenoma is **heterogeneity**. The tumor is composed of acini, tubules, strands, or sheets of cells. The epithelial cells are small and dark and may form spindle forms. These epithelial elements are intermingled with a loose, often myxoid stroma sometimes containing islands of apparent cartilage or, rarely, bone ([Fig. 15](#)). The evidence suggests that all of the diverse cell types within pleomorphic adenoma, including the stroma, are of myoepithelial derivation.







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 Figure 15-5 Pleomorphic adenoma. **A**, A well-demarcated tumor in the parotid gland. **B**, Low-power view showing the tumor's relationship with surrounding tissue. **C**, High-power view showing amorphous myxoid stroma resembling cartilage, with interspersed islands and cords of epithelial cells.  
 Lee, Department of Pathology, University of Texas Southwestern Medical Center,

#### *Warthin Tumor (Papillary Cystadenoma Lymphomatosum, Cystadenolymphoma)*

This infrequent benign tumor occurs virtually only in the region of the parotid gland and is thought to be trapped within a regional lymph node during embryogenesis. This tumor is generally a small, well-circumscribed mass. On transection often reveals mucin-containing cleftlike or cystic spaces within a soft gray background. Characteristic features: (1) a two-tiered epithelial layer lining the branching, cystic, or cleftlike spaces; (2) well-developed lymphoid tissue sometimes forming germinal centers. A recurrence rate of about 1% after complete excision. Multicentricity, or a second primary tumor. Malignant transformation is rare; about half of reported cases.

#### **SUMMARY** **Salivary Gland Diseases**

*Sialadenitis*: inflammation caused by infection (e.g. mumps, various bacteria) or autoimmune disease (as in Sjögren syndrome). *Pleomorphic adenoma (mixed salivary gland tumor)*: an infiltrative tumor composed of heterogeneous epithelial elements and an abundant stroma. *Warthin tumor*: benign tumor composed of epithelial cells and dense lymphoid tissue.





## ESOPHAGUS

Lesions of the esophagus run the gamut from bland esophagitis to lethal cancers, yet they evoke a similar and remarkably limited range of symptoms. All produce *dysphagia* (difficulty in swallowing), which is attributed either to deranged esophageal motor function or to narrowing or obstruction of the lumen. *Heartburn* (retrosternal burning pain) usually reflects regurgitation of gastric contents into the lower esophagus. Less commonly, *hematemesis* (vomiting of blood) and *melena* (blood in the stools) are evidence of severe inflammation, ulceration, or laceration of the esophageal mucosa. Massive hematemesis may reflect life-threatening rupture of esophageal varices.





## ANATOMIC AND MOTOR DISORDERS

Both esophageal anatomy and motor function may be affected secondarily by many esophageal disorders are described here. Infrequent conditions are listed in [Table 15-2](#).

### Achalasia

The term *achalasia* means "failure to relax," and in the present context, denotes incomplete relaxation of the lower esophageal sphincter in response to swallowing. This produces functional obstruction of the esophagus, with consequent dilatation of the esophageal body (Fig. 15-6). Manometric studies show three major abnormalities in achalasia: (1) aperistalsis, (2) failure of the lower esophageal sphincter to relax with swallowing, and (3) increased resting tone of the lower esophageal sphincter. In primary achalasia there is loss of intrinsic inhibitory innervation of the lower esophageal sphincter and the esophageal body. Secondary achalasia may arise from diverse pathologic processes that impinge on the esophagus; for example is Chagas disease, caused by *Trypanosoma cruzi*, which causes destruction of the myenteric plexus in the esophagus, duodenum, colon, and ureter. Disorders of the dorsal motor nuclei such as polio, and autonomic neuropathies may also cause secondary achalasia. *In most instances, however, achalasia occurs as a primary disorder of unknown cause.*

**Table 15-2. Selected (Infrequent) Anatomic Disorders of the Esophagus**

Disorder Clinical Presentation and Anatomy	
Stenosis	Adult with progressive dysphagia to solids and eventually to all foods; a lower esophageal narrowing; chronic inflammatory disease, including gastroesophageal reflux
Atresia, fistula	Newborn with aspiration, paroxysmal suffocation, pneumonia; esophageal atresia (absence of esophagus) and tracheoesophageal fistula may occur together
Webs, rings	Episodic dysphagia to solid foods; an (presumably) acquired mucosal web or mucosal and submucosal rings
Diverticula	Episodic food regurgitation, especially nocturnal; sometimes pain is present; an acquired outpocketing of the esophagus

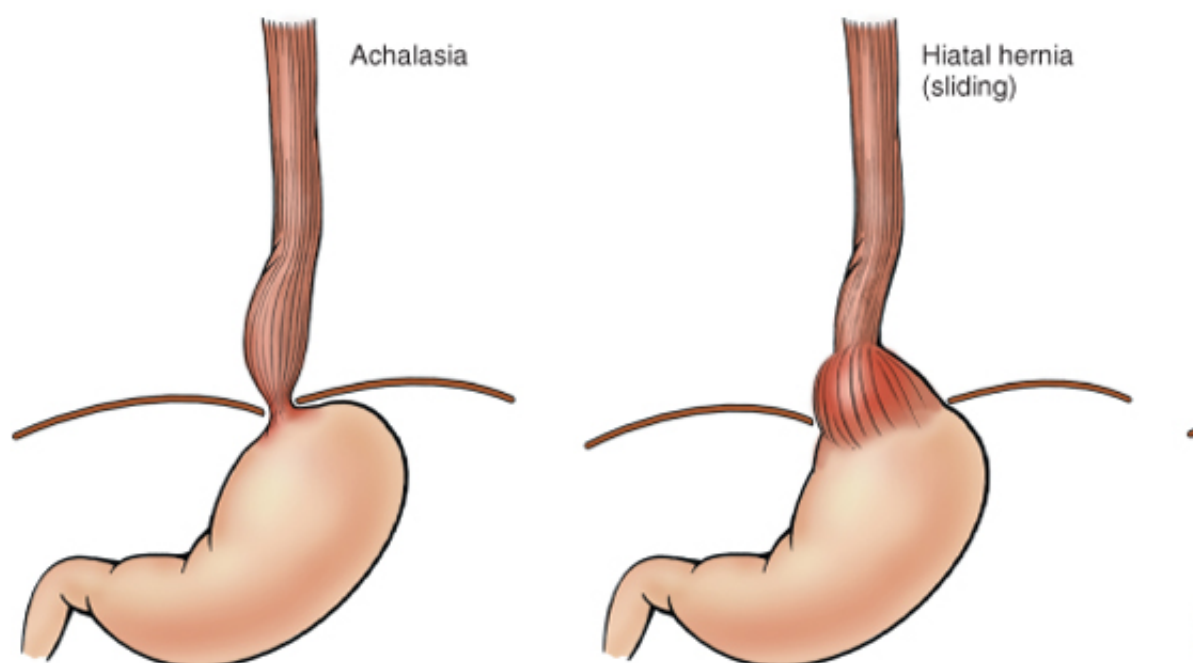


Figure 15-6 Achalasia and hiatal hernias. Comparison between sliding and paraesophageal.

In primary achalasia there is progressive dilation of the esophagus above the level of the lower esophagus. The esophagus may be of normal thickness, thicker than normal because of hypertrophy of the muscularis. Myenteric ganglia are usually absent from the body of the esophagus but may or may not be reduced at the esophageal sphincter. Inflammation in the location of the esophageal myenteric plexus is pathognomonic of achalasia. Achalasia is not a mucosal disease, stasis of food may produce mucosal inflammation and ulceration at the sphincter.

Achalasia is characterized clinically by progressive dysphagia and inability to completely convey food. Regurgitation and aspiration of undigested food may occur. It usually becomes manifest in young adults in childhood. The most serious aspect of this condition is the hazard of developing esophageal squamous metaplasia in about 5% of patients and typically at an earlier age than in those without achalasia.

### Hiatal Hernia

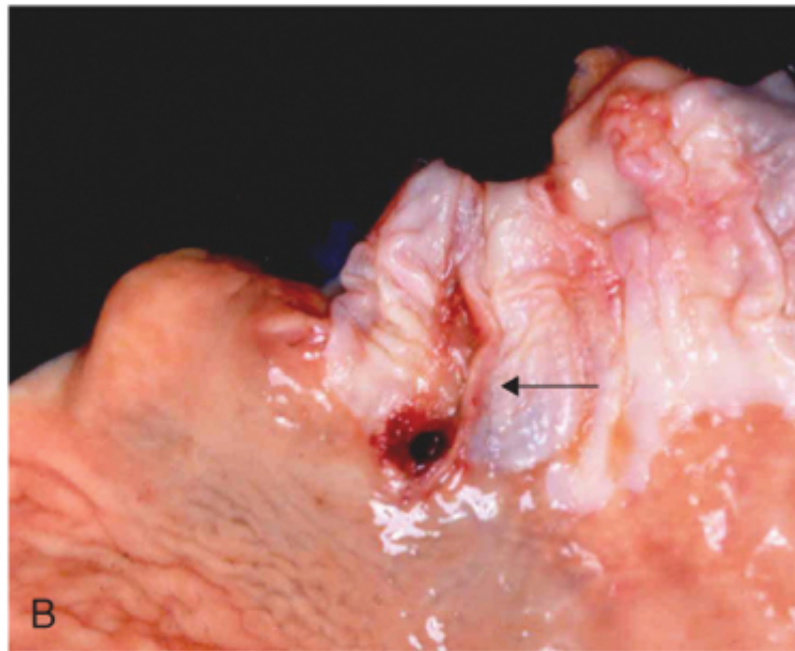
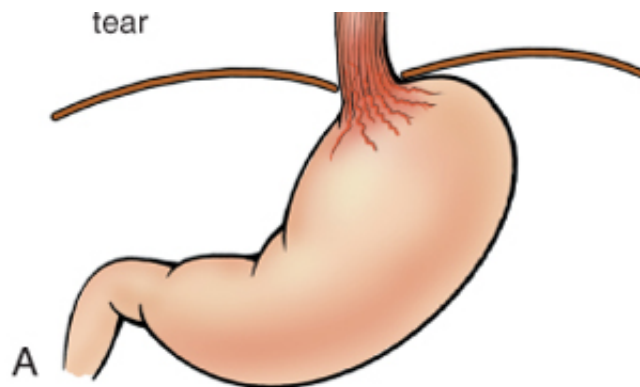
In hiatal hernia, separation of the diaphragmatic crura and widening of the space between the muscles permits a dilated segment of the stomach to protrude above the diaphragm. Two anatomic patterns are recognized: sliding, hernia and the nonaxial, or paraesophageal, hernia. The *sliding hernia* constitutes 95% of the hernias. The diaphragm creates a bell-shaped dilation, bounded below by the diaphragmatic narrowing. In this type, a portion of the stomach, usually along the greater curvature, enters the thorax through the widened hiatus. The anatomy, whether congenital or acquired, is unknown.

On the basis of radiographic studies, hiatal hernias are reported in 1% to 20% of adult subjects, in about 9% of these adults, however, suffer from heartburn or regurgitation of gastric juices into the esophagus as a result from incompetence of the lower esophageal sphincter than from the hiatal hernia per se and reflux (bending forward, lying supine) and obesity. Although most individuals with sliding hiatal hernia (discussed later), those with severe reflux esophagitis are likely to have a sliding hiatal hernia. Other hiatal hernias include mucosal ulceration, bleeding, and even perforation. Paraesophageal hernias become strangulated or obstructed.

### Lacerations (Mallory-Weiss Syndrome)

Longitudinal tears in the esophagus at the esophagogastric junction are termed *Mallory-Weiss tears*. They are usually seen in chronic alcoholics after a bout of severe retching or vomiting, but they may also occur during acute gastritis. The presumed pathogenesis is inadequate relaxation of the musculature of the lower esophageal sphincter during tearing of the esophagogastric junction at the moment of propulsive expulsion of gastric contents. A hiatal hernia is found in more than 75% of patients with Mallory-Weiss tears. Notably, almost half of individuals with gastrointestinal bleeding attributable to a Mallory-Weiss tear have no antecedent history of nausea or vomiting. One must hypothesize that normal variability in intra-abdominal pressure can be transduced through a Mallory-Weiss tear. Tears may involve only the mucosa or may penetrate the wall. Infection of the ulcer or to mediastinitis.





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Figure 15-7 Esophageal lacerations (Mallory-Weiss syndrome). **A**, Longitudinal tears in the esophagogastric junction. **B**, Longitudinal lacerations oriented in the axis of the esophageal lumen (arrow), extending from the esophageal mucosa into the lumen. Photographed by Dr. Richard Harruff, King County Medical Examiner's Office, Seattle, Wa.

Esophageal lacerations account for 5% to 10% of upper gastrointestinal bleeding episodes. Most heal without surgical intervention, but life-threatening hematemesis may occur. Even with severe blood transfusions, vasoconstrictive medications, and sometimes balloon tamponade, is usually all that is required with minimal to no residual problems.



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## VARICES

One of the few potential sites for communication between the intra-abdominal splanchnic circulation and the systemic venous circulation is through the esophagus. When portal venous blood flow into the liver is impeded by cirrhosis or other causes, the resultant portal hypertension induces the formation of collateral bypass channels wherever the portal and systemic systems communicate. Portal blood flow is thereby diverted through the stomach veins into the plexus of esophageal subepithelial and submucosal veins, thence into the azygos veins and the superior vena cava. The increased pressure in the esophageal plexus produces dilated tortuous vessels called varices. *Persons with cirrhosis develop varices at a rate of 5% to 15% per year, so that varices are present in approximately two-thirds of all cirrhotic patients.* In the United States, esophageal varices are most often associated with alcoholic cirrhosis.

### Morphology

Varices appear as tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach. The net effect is irregular protrusion of the overlying mucosa into the lumen, although varices are collapsed in surgical or postmortem specimens (Fig. 15-8). When the varix is unruptured, the mucosa may be normal, but often it is eroded and inflamed because of its exposed position, further weakening the tissue support of the dilated veins.

Variceal rupture produces massive hemorrhage into the lumen, *as well as suffusion of blood into the esophageal wall.* Varices produce no symptoms until they rupture. Among persons with advanced cirrhosis of the liver, half the deaths result from rupture of a varix, either as a direct consequence of the hemorrhage or from the hepatic coma triggered by the hemorrhage. However, even when varices are present, they account for less than half of all episodes of hematemesis. Bleeding from concomitant gastritis, peptic ulcer, or esophageal laceration accounts for most of the remainder.







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 Figure 15-8 Esophageal varices: a view of the everted esophagus and gastroesophageal junction, showing dilated submucosal veins (varices). The blue-colored varices have collapsed in this postmortem specimen.

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The conditions leading to initial rupture of a varix are unclear: silent erosion of overlying thinned mucosa, increased tension in progressively dilated veins, and vomiting with increased intra-abdominal pressure are likely to be involved. One-half of those affected are found to have coexistent hepatocellular carcinoma, suggesting that a progressive decrease in hepatic functional reserve from tumor growth enhances the likelihood of variceal rupture. Once begun, variceal hemorrhage subsides spontaneously in only 50% of cases; endoscopic injection of thrombotic agents (sclerotherapy) or balloon tamponade is often required. When varices bleed, 20% to 30% of patients die during the first episode. Among those who survive, rebleeding occurs in approximately 70% within 1 year, with a similar rate of mortality for each episode.



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## ESOPHAGITIS

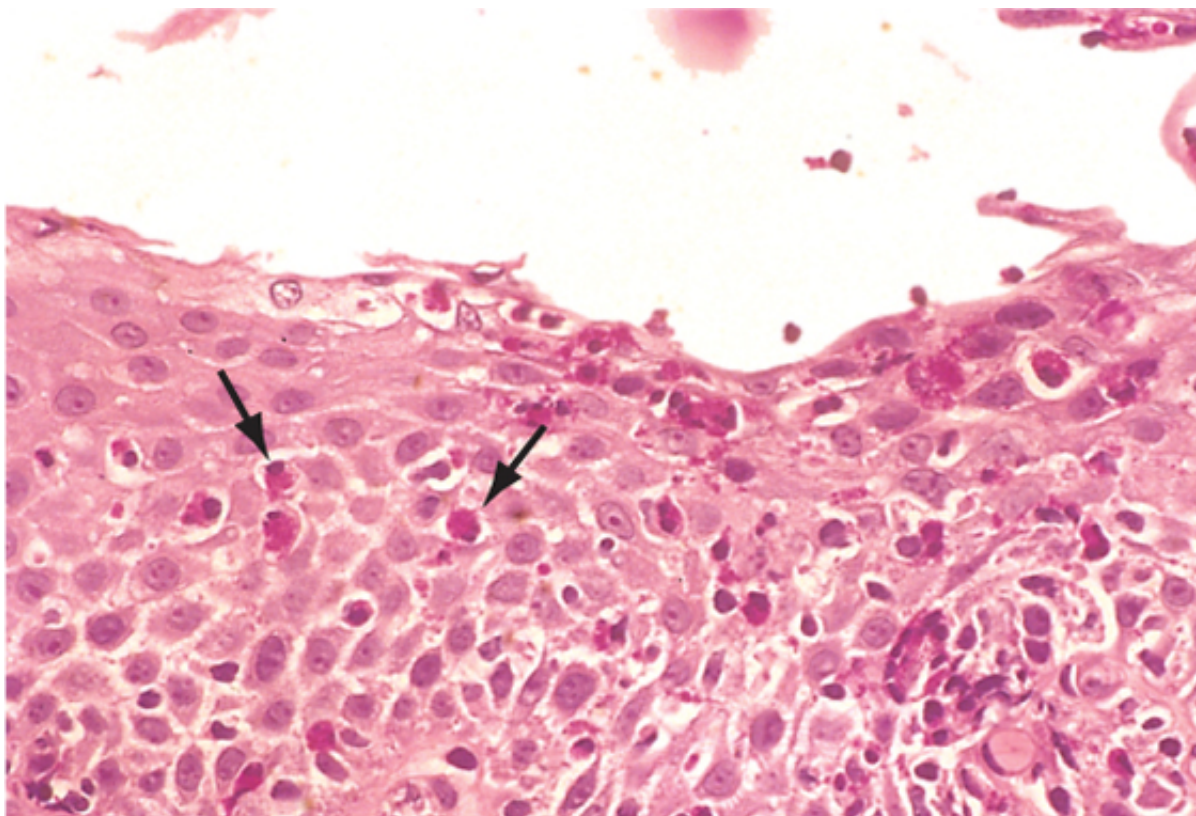
Injury to the esophageal mucosa with subsequent inflammation is a common condition worldwide. origins: prolonged gastric intubation, uremia, ingestion of corrosive or irritant substances, and radiation. In northern Iran the prevalence of esophagitis is more than 80%; it is also extremely high in regions of the world where the cause is unknown. *The overwhelming preponderance of cases in Western countries are attributable to reflux.* Gastroesophageal reflux disease, as it is known clinically, affects about 0.5% of the US adult population. Heartburn is the dominant symptom. There are many presumed contributory factors:

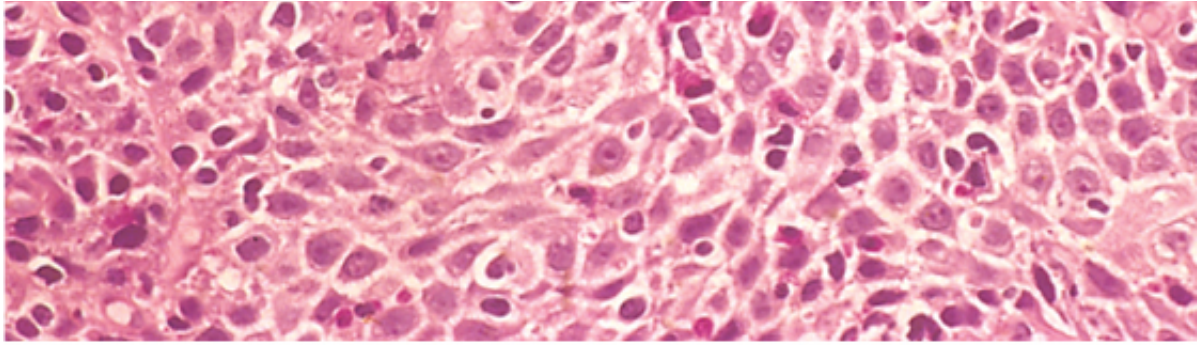
Decreased efficacy of esophageal antireflux mechanisms. Central nervous system depression may be some of the contributing causes, but most often no obvious etiology is identifiable. Inadequately cleared refluxed material. The presence of a sliding hiatal hernia. Increased gastric volume, contributing to reflux. Impaired reparative capacity of the esophageal mucosa by prolonged exposure to irritants.

Any one of these influences may assume primacy in an individual case, but more than one is likely to be operative.

### Morphology

The anatomic changes depend on the causative agent and on the duration and severity. Mild esophagitis may appear macroscopically as simple hyperemia, with virtually no histologic changes. In contrast, the mucosa in severe esophagitis shows confluent epithelial erosions or ulcers extending into the submucosa. Three histologic features are characteristic of uncomplicated **reflux esophagitis**, although only one or two may be present: (1) eosinophils, with or without neutrophils; (2) basal zone hyperplasia; and (3) elongation of lamina propria papillae. Intraepithelial lymphocytes are markers of more severe injury.





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 Figure 15-9 Reflux esophagitis showing the superficial portion of the mucosa. Numerous eosinophils (arrows) are present. The squamous epithelium has not undergone complete maturation because of ongoing inflammation.

### Clinical Features

The dominant manifestation of reflux disease is heartburn, sometimes accompanied by regurgitation. Symptoms are punctuated by attacks of severe chest pain mimicking a heart attack. *The severity of symptoms is proportional to the presence and degree of anatomic esophagitis.* Though largely limited to adults older than age 40, reflux disease can also affect infants and children. The potential consequences of severe reflux esophagitis are bleeding, development of Barrett's esophagus, with its predisposition to malignancy.



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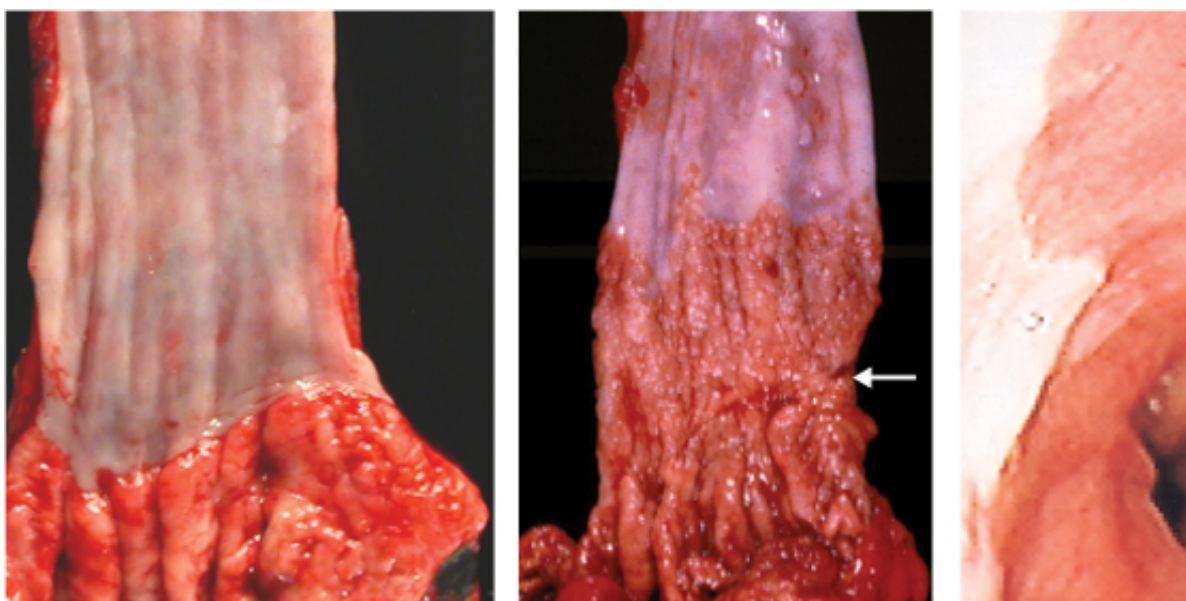
## BARRETT ESOPHAGUS

*Barrett esophagus is defined as the replacement of the normal distal stratified squamous mucosa containing goblet cells.* It is a complication of long-standing gastroesophageal reflux, occurring in persistent symptomatic reflux disease. However, Barrett esophagus has been detected in about 1% of the general population. It is unclear why individuals with few symptoms and little inflammation develop Barrett esophagus, while others have erosive esophagitis without Barrett esophagus. Barrett esophagus affects males more than females and is much more common in whites than in other races. Prolonged and recurrent gastroesophageal reflux and eventually ulceration of the squamous epithelial lining. Healing occurs by ingrowth of progenitor cells. The microenvironment of an abnormally low pH in the distal esophagus caused by acid reflux, the cell: Metaplastic columnar epithelium is thought to be more resistant to injury from refluxing gastric contents. This columnar epithelium is not a typical intestinal epithelium, as absorptive enterocytes are not observed.

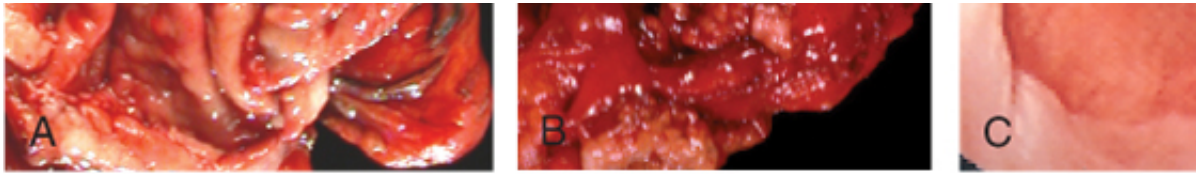
Ulcer and stricture may develop as a complication of Barrett esophagus. However, *the chief clinical risk for the development of adenocarcinoma.* Persons with Barrett esophagus have a 30- to 100-fold increased risk of developing adenocarcinoma than do normal populations, the greatest risk being associated with high-grade dysplasia. Endoscopic surveillance with esophageal biopsy is recommended for Barrett esophagus sufferers. Prevention requires therapeutic interventions, such as surgery, photodynamic ablation, or very careful surveillance.

### Morphology

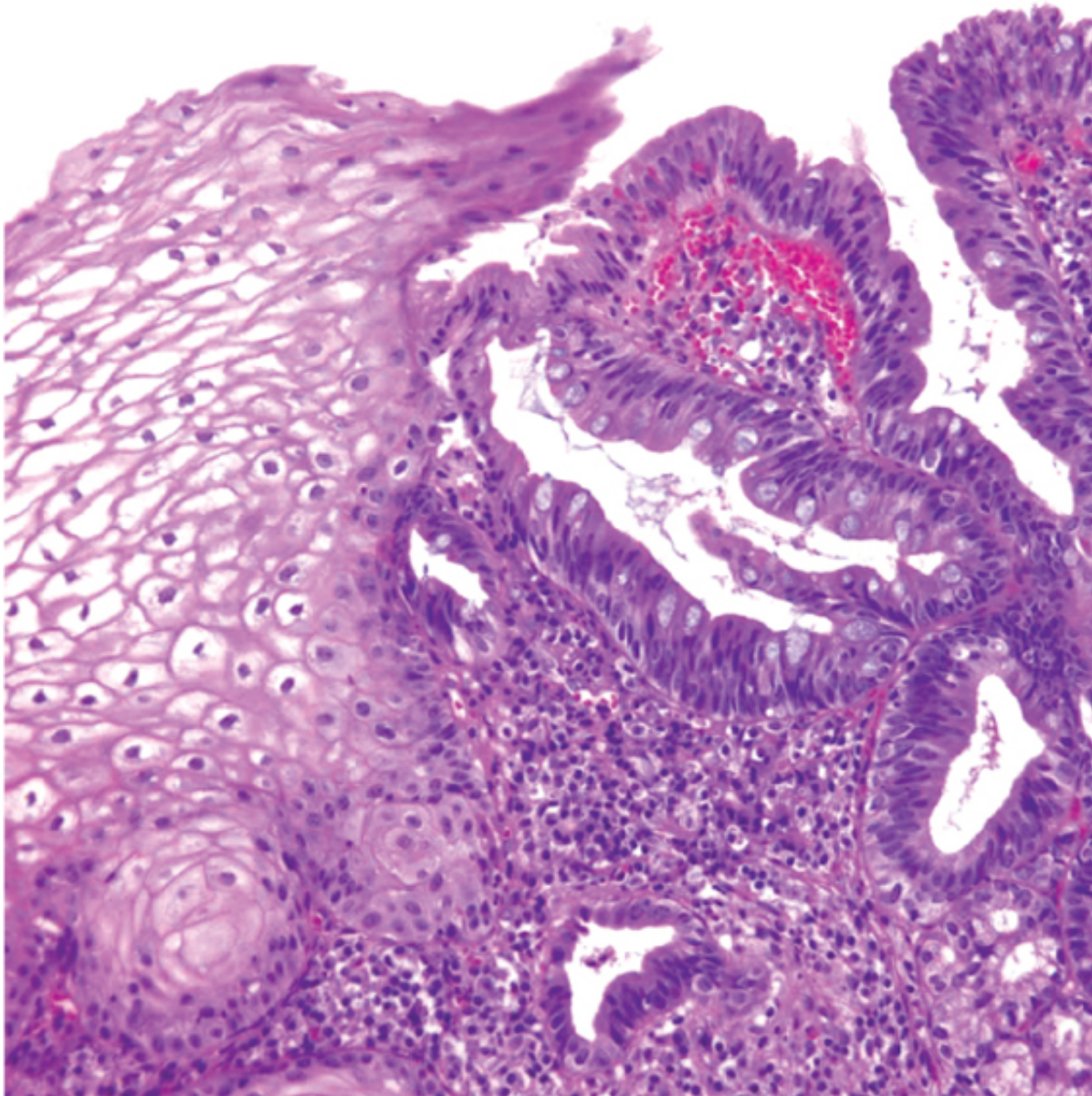
Barrett esophagus is apparent as a salmon-pink, velvety mucosa between the normal stratified squamous mucosa and the more lush light brown gastric mucosa (Fig. 15-10). It may extend up from the gastroesophageal junction, as an irregular circumferential band of squamocolumnar junction cephalad, or as isolated patches (islands) in the distal esophagus. The changes are not as important as the presence in the anatomic esophagus of metaplastic columnar epithelium containing goblet cells. **Microscopically, the esophageal squamous epithelium is replaced by metaplastic columnar epithelium**, as depicted in Figure 15-11. **Barrett mucosa is variable from one site to the next**, often necessitating repeated endoscopy and biopsy for diagnosis. Critical to the pathologic evaluation of individuals with Barrett mucosa is the identification of dysplastic changes in the mucosa that may be precursors of cancer.







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 Figure 15-10 Barrett esophagus. **A-B**, Gross view of distal esophagus (*top*) and proximal stomach (*bottom*) showing the granular zone of Barrett esophagus (*arrow*). **C**, Endoscopic view showing red velvety gastrointestinal-type mucosa. Note paler squamous esophageal mucosa. (**C**, Courtesy of Dr. F. Farrar, Brigham and Women's Hospital)



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 Figure 15-11 Barrett esophagus. Microscopic view showing squamous mucosa (*left*) and intestinal-type columnar mucosa (*right*).







## ESOPHAGEAL CARCINOMA

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**Table 15-3. Risk Factors for Squamous Cell Carcinoma of the Esophagus**

<b>Esophageal Disorders</b>
Long-standing esophagitis
Achalasia
Plummer-Vinson syndrome (esophageal webs, microcytic hypochromic anemia, atrophic glossitis)
<b>Life-style</b>
Alcohol consumption
Tobacco abuse
<b>Dietary</b>
Deficiency of vitamins (A, C, riboflavin, thiamine, pyridoxine)
Deficiency of trace metals (zinc, molybdenum)
Fungal contamination of foodstuffs
High content of nitrites/nitrosamines
<b>Genetic Predisposition</b>
Tylosis (hyperkeratosis of palms and soles)

Benign tumors may arise in the esophagus from both the squamous mucosa and underlying mesenchyme. However, these are overshadowed by cancer of the esophagus, of which there are two types: *squamous cell carcinomas* and *adenocarcinomas*. Worldwide, squamous cell carcinomas constitute 90% of esophageal cancers, but in the United States there has been a very large increase (three- to fivefold in the last 40 years) in the incidence of adenocarcinomas associated with Barrett esophagus. Indeed, this form of cancer has surpassed squamous cell carcinoma in incidence in the United States. Adenocarcinoma arising in Barrett esophagus is more common in whites than in blacks. By contrast, squamous cell carcinomas are more common in blacks worldwide. There are striking and puzzling differences in the geographic incidence of esophageal carcinoma. In the United States, there are about 6 new cases per 100,000 population per year, accounting for 1% to 2% of all cancer deaths. In regions of Asia extending from the northern provinces of China to the Caspian littoral in Iran, the prevalence is well over 100 per 100,000, and 20% of cancer deaths are caused by esophageal carcinoma (mainly squamous cell type).

### **Squamous Cell Carcinoma**

An important contributing variable is retarded passage of food through the esophagus, prolonging mucosal exposure to potential carcinogens such as those contained in tobacco and alcoholic beverages (Table 15-3). There is a well-defined predisposing role for chronic esophagitis, which is often the consequence of alcohol and tobacco use. These two agents are associated with the majority of squamous cell carcinoma in Europe and the United States. However, other influences, perhaps in the diet, must underlie the very high incidence of this tumor among the orthodox Moslems of Iran, who neither drink nor smoke. The high levels of nitrosamines and fungi contained in some foods probably account for the very high incidence of this tumor in some regions of China. A strong association with human papillomavirus occurs only in high-incidence areas. Abnormalities affecting the *p16/INK4* tumor suppressor gene and the epidermal growth factor receptor are frequently present in squamous cell carcinoma of the esophagus. Mutations in *p53* are detected in as many as 50% of these tumors and are generally correlated with the use of tobacco and alcohol. Unlike in colon carcinomas, mutations in the *KRAS* and *APC* genes are uncommon.

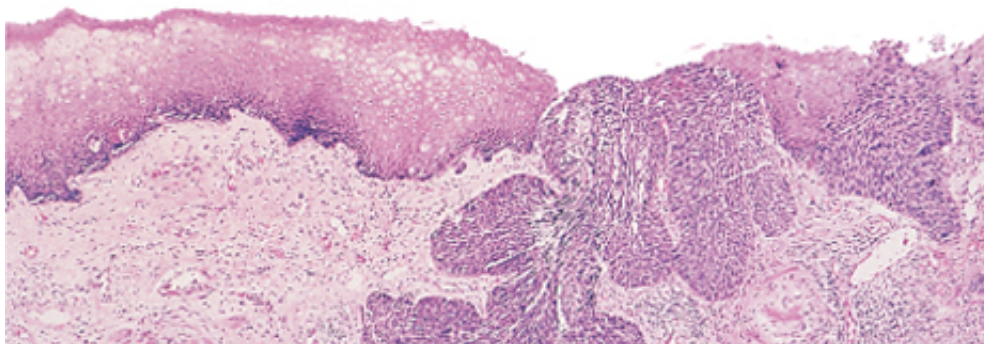


Mutations in the *K-RAS* and *APC* genes are uncommon.

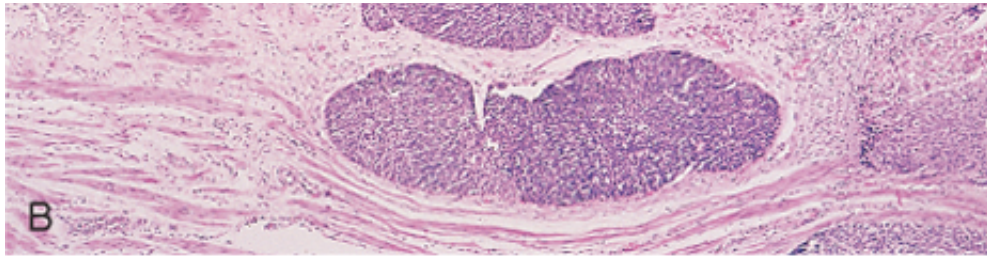
### Morphology

Squamous cell carcinomas are usually preceded by a long prodrome of mucosal **epithelial dysplasia** followed by **carcinoma in situ** and, ultimately, by the emergence of **invasive cancer**. Early overt lesions appear as small, gray-white, plaquelike thickenings or elevations of the mucosa. In months to years, these lesions become tumorous, taking one of three forms: (1) **polypoid exophytic masses** that protrude into the lumen; (2) necrotizing cancerous **ulcerations** that extend deeply and sometimes erode into the respiratory tree, aorta, or elsewhere (Fig. 15-12); and (3) **diffuse infiltrative neoplasms** that cause thickening and rigidity of the wall and narrowing of the lumen. Whichever the pattern, about 20% arise in the cervical and upper thoracic esophagus, 50% in the middle third, and 30% in the lower third.

### Adenocarcinoma







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Figure 15-12 **A**, Large ulcerated squamous cell carcinoma of the esophagus. **B**, Low power view of cancer invasion of the submucosa.

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*Barrett esophagus is the only recognized precursor of esophageal adenocarcinoma.* The development of adenocarcinomas from Barrett esophagus is a multistep process that unfolds over many years. The degree of dysplasia is the strongest predictor of the progression to cancer. Individuals with low-grade dysplasia have very low rates of progression to adenocarcinomas but the progression to cancer may be 10% or more per year in individuals with high-grade dysplasia. Overall, the risk for developing adenocarcinoma varies from 30-fold to more than 100-fold above normal. In Barrett esophagus tissue there is increased cell proliferation, and chromosomal abnormalities become apparent in high-grade dysplasia. Mutations in *p53* progressively accumulate, and aneuploidy is commonly found. Additional genetic abnormalities, such as alterations in *HER-2/NEU* and *β-catenin*, are present in the carcinomas, but there are no specific markers that precisely identify the transition from high-grade dysplasia to cancer.

### Morphology

Adenocarcinomas seem to arise from dysplastic mucosa in the setting of **Barrett esophagus**. Unlike squamous cell carcinomas, they are usually in the distal one-third of the esophagus and may invade the subjacent gastric cardia. Initially appearing as flat or raised patches on an otherwise intact mucosa, they may develop into **large nodular masses** or show deeply **ulcerative** or **diffusely infiltrative** features. Microscopically, most tumors are mucin-producing glandular tumors showing intestinal-type features, in keeping with the morphology of the preexisting metaplastic mucosa.

### Clinical Features

Esophageal carcinoma is insidious in onset and produces dysphagia and obstruction gradually and late. Weight loss, anorexia, fatigue, and weakness appear, followed by pain, usually related to swallowing. Diagnosis is usually made by imaging techniques and endoscopic biopsy. Because these cancers extensively invade the rich esophageal lymphatic network and adjacent structures relatively early in their development, surgical excision is rarely curative. Thus, much emphasis is placed on surveillance procedures for individuals with persistent manifestations of chronic esophagitis or known Barrett esophagus. Esophageal cancer confined to the mucosa or submucosa is amenable to surgical treatment.

### SUMMARY

**Diseases of the Esophagus**  
*Hiatal hernia*: protrusion of segment of the stomach above the diaphragm; occasionally results in reflux and esophagitis.  
*Lacerations (Mallory-Weiss syndrome)*: longitudinal tears at the esophago-gastric junction caused by severe retching and vomiting; may cause upper GI bleeding.  
*Varices*: tortuous dilated veins at the distal esophagus

and proximal stomach; caused by increased portal pressure (most often due to cirrhosis), leading to increased pressure in the esophageal venous plexus; may cause severe bleeding. *Esophagitis*: Inflammation of the esophageal mucosa most often caused by reflux of gastric contents; inflammatory infiltrate often contains abundant eosinophils. *Barrett esophagus*: replacement of stratified squamous epithelium of distal esophagus by metaplastic columnar epithelium containing goblet cells; associated with gastroesophageal reflux in ~15% of cases; main harmful consequence is the development of dysplasia and 30- to 100-fold increased risk for adenocarcinoma. *Esophageal carcinoma*:

Squamous cell carcinomas arise from dysplastic epithelium, associated with esophagitis, smoking; may be locally invasive. Adenocarcinomas arise usually in Barrett esophagus, now more frequent in the US.





## STOMACH

Gastric disorders frequently cause clinical disease, ranging from bland chronic gastritis to the anything but bland gastric carcinoma. Gastric infection with *Helicobacter pylori* represents the most common gastrointestinal infection. Occasionally, congenital anomalies are encountered; these are summarized in [Table 15-4](#).

Gastric disorders give rise to symptoms similar to esophageal disorders, primarily *heartburn* and *vague epigastric pain*. With breach of the gastric mucosa and bleeding, *hematemesis* or *melen* may ensue. Unlike esophageal bleeding, however, blood quickly congeals and turns brown in the acid environment of the stomach lumen. Vomited blood hence has the appearance of coffee grounds.





## GASTRITIS

**Table 15-4. Congenital Gastric Anomalies**

Condition	Comment
Pyloric stenosis	1 in 300-900 live births
	Male-to-female ratio 3:1
	Pathology: muscular hypertrophy of pyloric smooth muscle wall
	Symptoms: persistent, nonbilious projectile vomiting in young infant
Diaphragmatic hernia	Rare
	Pathology: herniation of stomach and other abdominal contents into thorax through diaphragm
	Symptoms: acute respiratory distress in newborn
Gastric heterotopia	Uncommon
	Pathology: a nidus of gastric mucosa in the esophagus or small intestine ("ectopic gastric mucosa")
	Symptoms: asymptomatic, or an anomalous peptic ulcer in adult

This diagnosis is both overused and often missed—overused when it is applied loosely to any transverse section of the stomach wall in the absence of validating evidence, and missed because most persons with chronic gastritis are asymptomatic. The term *gastritis* implies *inflammation of the gastric mucosa*. By far the majority of cases are *chronic gastritis*, but occasional acute gastritis is also encountered. These two conditions are discussed below.

### Chronic Gastritis

Chronic gastritis is defined as the presence of chronic inflammatory changes in the mucosa leading to epithelial metaplasia. It is notable for distinct causal subgroups and for patterns of histologic alterations. In the Western world, the prevalence of histologic changes indicative of chronic gastritis is low in most life.

#### Pathogenesis

By far the most important etiologic association is chronic infection by the bacillus *H. pylori*. This organism has the highest infection rates in developing countries. American adults older than age 50 show prevalence where the infection is endemic, it seems to be acquired in childhood and persists for decades. Most persons with *H. pylori* have associated gastritis but are asymptomatic. (Robin Warren, a pathologist, and Barry Marshall, a physician, received the 2005 Nobel prize in Medicine for their identification in 1982 of *H. pylori*, or

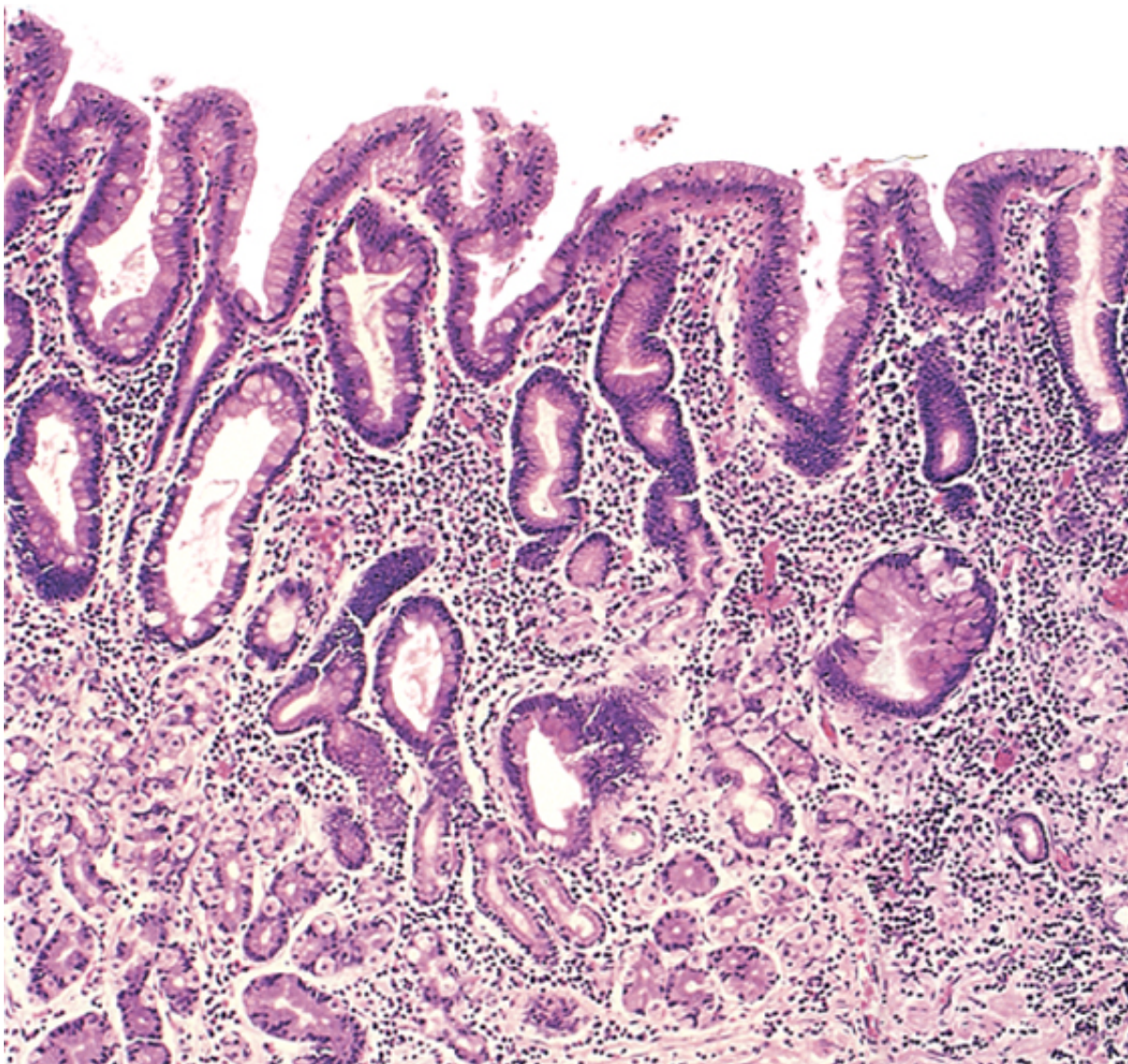
*H. pylori* is a noninvasive, non-spore-forming, S-shaped gram-negative rod measuring approximately 3–5  $\mu$ m. The mechanisms by which *H. pylori* causes tissue injury are discussed in detail in the section below on Peptic Ulcer Disease. As a result of the combined influence of bacterial enzymes and toxins and release of noxious chemicals, after initial exposure to *H. pylori*, gastritis may develop in two patterns: (1) an antral-type with high acid production and development of duodenal ulcer, and (2) a pangastritis with multifocal mucosal atrophy, with low acid production and development of adenocarcinoma. Persons with chronic gastritis and *H. pylori* usually improve symptomatically with proton pump inhibitors. Improvement in the underlying chronic gastritis may take much longer. Relapses are common if the organism is not eradicated.

Other forms of chronic gastritis are much less common in the United States. *Autoimmune gastritis* is a rare condition in which cases of chronic gastritis, results from the production of autoantibodies to the gastric gland parietal cells, leading to atrophy of the gastric mucosa. The enzyme  $H^+, K^+$ -ATPase. The autoimmune injury leads to gland destruction and mucosal atrophy, with loss of intrinsic factor production. The resultant deficiency of intrinsic factor leads to *pernicious anemia*, discussed in Chapter 20. It is seen most often in Scandinavia, in association with other autoimmune disorders such as Hashimoto's thyroiditis (Chapter 20).

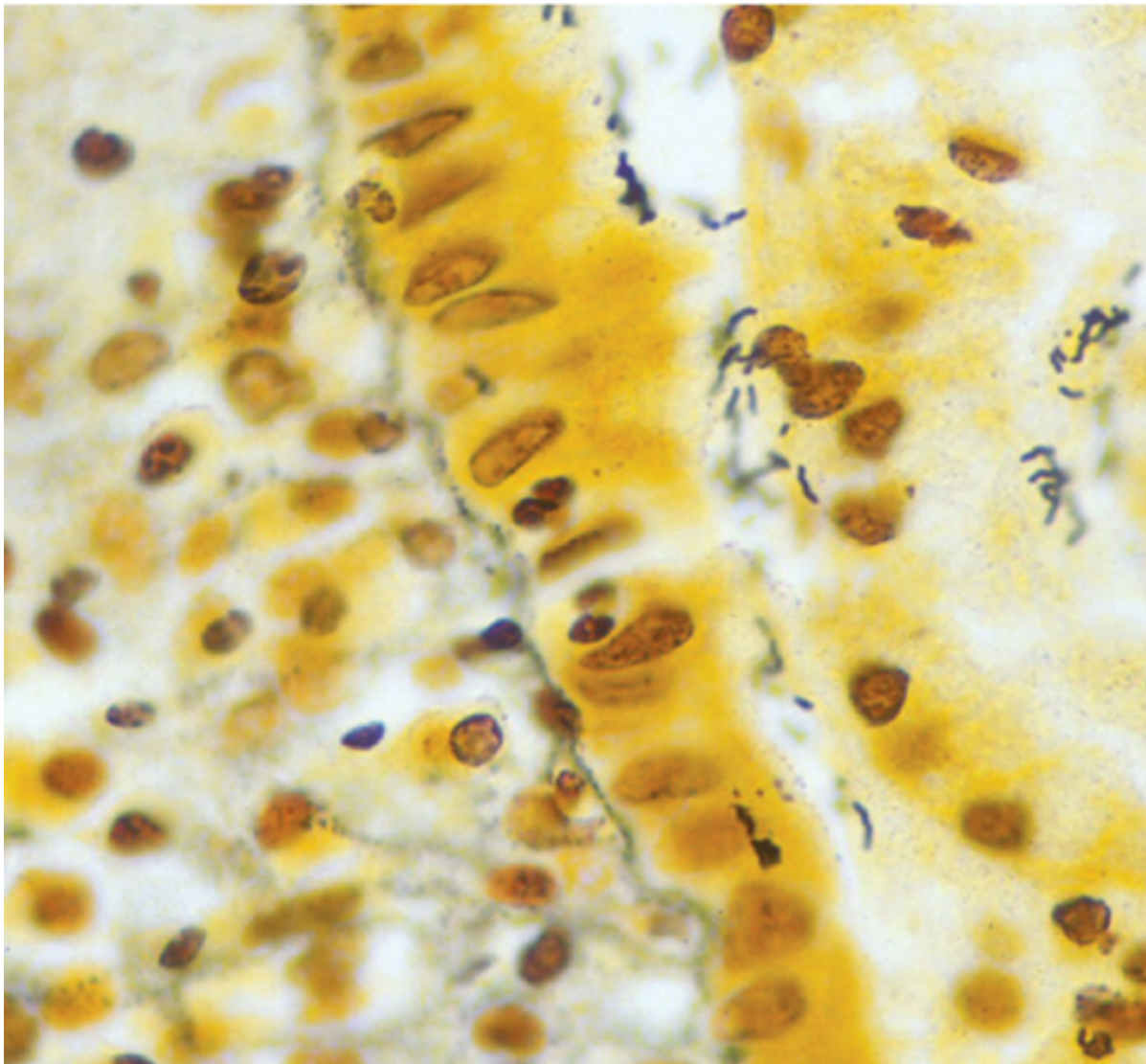


### Morphology

Regardless of the cause or histologic distribution of chronic gastritis, the inflammatory lymphocytic and plasma cell infiltrate in the lamina propria (Fig. 15-13), occasional neutrophilic inflammation of the neck region of the mucosal pits. The inflammation causes variable gland loss and mucosal atrophy. When present, *H. pylori* organisms are found in the mucus layer overlying the superficial mucosal epithelium (Fig. 15-14). In the autoimmune form, the destruction of parietal cells is particularly prominent. Two additional features are of note. **Intestinal metaplasia** is the replacement of gastric epithelium with columnar and goblet cells of intestinal type, because gastrointestinal-type carcinomas (see later) seem to arise from **dysplasia** of the intestinal-type epithelium. Second, *H. pylori*-induced proliferation of **lymphoid tissue** within the lamina propria is implicated as a precursor of gastric lymphoma.



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Figure 15-13 Chronic gastritis, showing partial replacement of the gastric mucosal epithelium by intestinal metaplasia (right). The lamina propria contains a dense infiltrate of lymphocytes and plasma cells (right).



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 Figure 15-14 *Helicobacter pylori* gastritis. A Steiner silver stain demonstrates the numerous darkly stained *Helicob*  
 gastric epithelial cells. There is no tissue invasion by bacteria. (Courtesy of Dr. Melissa Upton, Department of F  
 Washington.)

### *Clinical Features*

Chronic gastritis usually causes few or no symptoms; upper abdominal discomfort and nausea an  
 parietal cell loss occurs in the setting of autoimmune gastritis, hypochlorhydria or achlorhydria (re  
 hydrochloric acid) and hypergastrinemia are characteristically present. Individuals with chronic ga  
 hypochlorhydric, but because parietal cells are never completely destroyed, these persons do not  
 anemia. Serum gastrin levels are either normal or only modestly elevated. Most important is the r  
 development of peptic ulcer and gastric carcinoma. Most individuals with a peptic ulcer, whether c  
 infection. The long-term risk of gastric carcinoma for persons with *H. pylori*-associated chronic ga  
 to the normal population. For autoimmune gastritis, the risk for cancer is in the range of 2% to 4%  
 above that of the normal population.

### **Acute Gastritis**

*Acute gastritis is an acute mucosal inflammatory process, usually of a transient nature.* The inflam  
 hemorrhage into the mucosa and, in more severe circumstances, by sloughing of the superficial n  
 erosive form of the disease is an important cause of acute gastrointestinal bleeding.



### Pathogenesis

The pathogenesis is poorly understood, in part because normal mechanisms for gastric mucosal protection and gastric acid secretion. Gastritis is frequently associated with:

Heavy use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin  
Excessive smoking  
Treatment with cancer chemotherapeutic drugs  
Uremia  
Systemic infections (e.g., *S. aureus*, *Candida*, *CMV*, *EBV*, *H. pylori*, *M. tuberculosis*, *Parvovirus B19*, *Toxoplasma gondii*, *Yersinia enterocolitica*)  
Burns, surgery  
Ischemia and shock  
Suicide attempts with acids and alkali  
Mechanical trauma  
Bilious material after distal gastrectomy

One or more of the following influences are thought to be operative in these varied settings: disruption of the mucosal barrier, stimulation of acid secretion with hydrogen ion back-diffusion into the superficial epithelium, decreased mucosal blood flow, decreased turnover of superficial epithelial cells, reduced mucosal blood flow, and direct damage to the epithelium. Not all are synergistic. Finally, acute infection with *H. pylori* induces neutrophilic inflammation of the gastric mucosa. The condition is usually of the notice of the individual.

### Morphology

Acute gastritis ranges from extremely localized (as occurs in NSAID-induced injury) to involvement of the entire mucosal thickness with hemorrhage and ulceration. Superficial inflammation to involvement of the entire mucosal thickness with hemorrhage and ulceration. Concurrent erosion and hemorrhage are readily visible by endoscopy and termed acute erosive gastritis. All variants are marked by mucosal edema and an inflammatory infiltrate of neutrophils and mononuclear chronic inflammatory cells. Regenerative replication of epithelial cells in the gastric mucosa. Provided that the noxious event is short lived, acute gastritis may disappear within days, with restitution of the normal mucosa.

### Clinical Features

Depending on the severity of the anatomic changes, acute gastritis may be entirely asymptomatic or may present as nausea and vomiting, or may present as overt hematemesis, melena, and potentially fatal blood loss. *of hematemesis, particularly in alcoholics*. Even in certain other settings, the condition is quite common. For example, patients who take daily aspirin<sup>®</sup> for rheumatoid arthritis develop acute gastritis at some time in their course, and the risk of gastric bleeding from NSAID-induced gastritis is dose related, thus increasing the likelihood of long-term use of such drugs.



## GASTRIC ULCERATION

*Ulcers* of the alimentary tract are defined histologically as a breach in the mucosa that extends through the submucosa or deeper. This is to be contrasted to *erosions*, in which there is a breach in the epithelium that heals within days, whereas healing of ulcers takes much longer. Although ulcers may occur anywhere in the gastrointestinal tract, the most common are the peptic ulcers that occur in the duodenum and stomach. Here we discuss peptic ulcers.

### Peptic Ulcers

Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to acidic peptic juices. At least 98% of peptic ulcers are either in the first portion of the duodenum or the stomach.

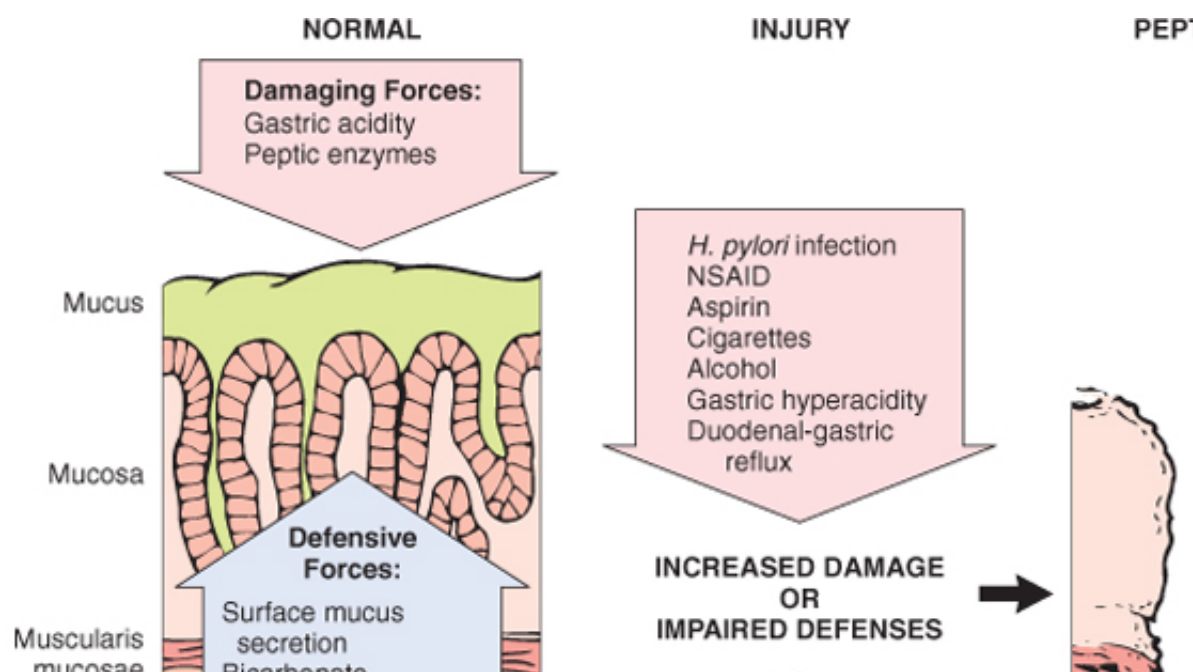
#### Epidemiology

Peptic ulcers are remitting, relapsing lesions that are most often diagnosed in middle-aged to older adults, but they can be evident in young adult life. They often appear without obvious precipitating influences and may be a marker for active disease. *Even with healing, however, the propensity to develop peptic ulcers remains, in part, because of H. pylori.* Thus, it is difficult to obtain accurate data on the prevalence of active disease. Best estimates for the general population, 6% to 14% of males and 2% to 6% of females have peptic ulcers. The male/female ratio is about 1.5/1. In both men and women in the United States, the lifetime risk of developing peptic ulcer disease is about 10%.

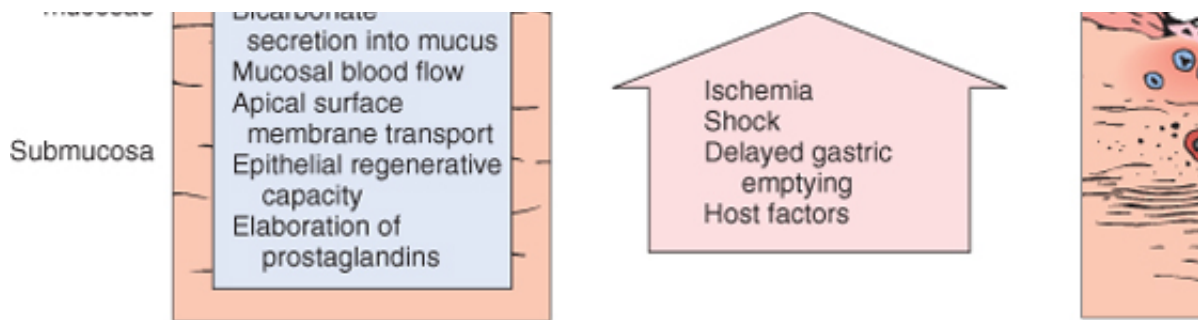
Genetic or racial influences seem to have little or no role in the causation of peptic ulcers. Duodenal ulcers are associated with alcoholic cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, and hyperparathyroidism. Conditions, hypercalcemia, whatever its cause, stimulates gastrin production and therefore acid secretion.

#### Pathogenesis

Two conditions are key for the development of peptic ulcers: (1) *H. pylori* infection, which has a strong association with the development, and (2) mucosal exposure to gastric acid and pepsin. Nevertheless, many aspects of the pathogenesis remain murky. It is best perhaps to consider that peptic ulcers are created by an imbalance between the mucosal defenses and the damaging forces that overcome such defenses (Fig. 15-15). Both sides of the imbalance are discussed below.







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Figure 15-15 Aggravating causes of, and defense mechanisms against, peptic ulceration. The right panel shows the resulting tissue changes: necrosis (N), inflammation (I), granulation tissue (G), and fibrosis (S).

*H. pylori* infection is the most important condition in the pathogenesis of peptic ulcer. The infection is associated with duodenal ulcers and in about 70% of those with gastric ulcers. Furthermore, antibiotic treatment of ulcers tends to prevent their recurrence. Hence, much interest is focused on the possible role of the spiral organism in tipping the balance of mucosal defenses. Here are the possible mechanisms:

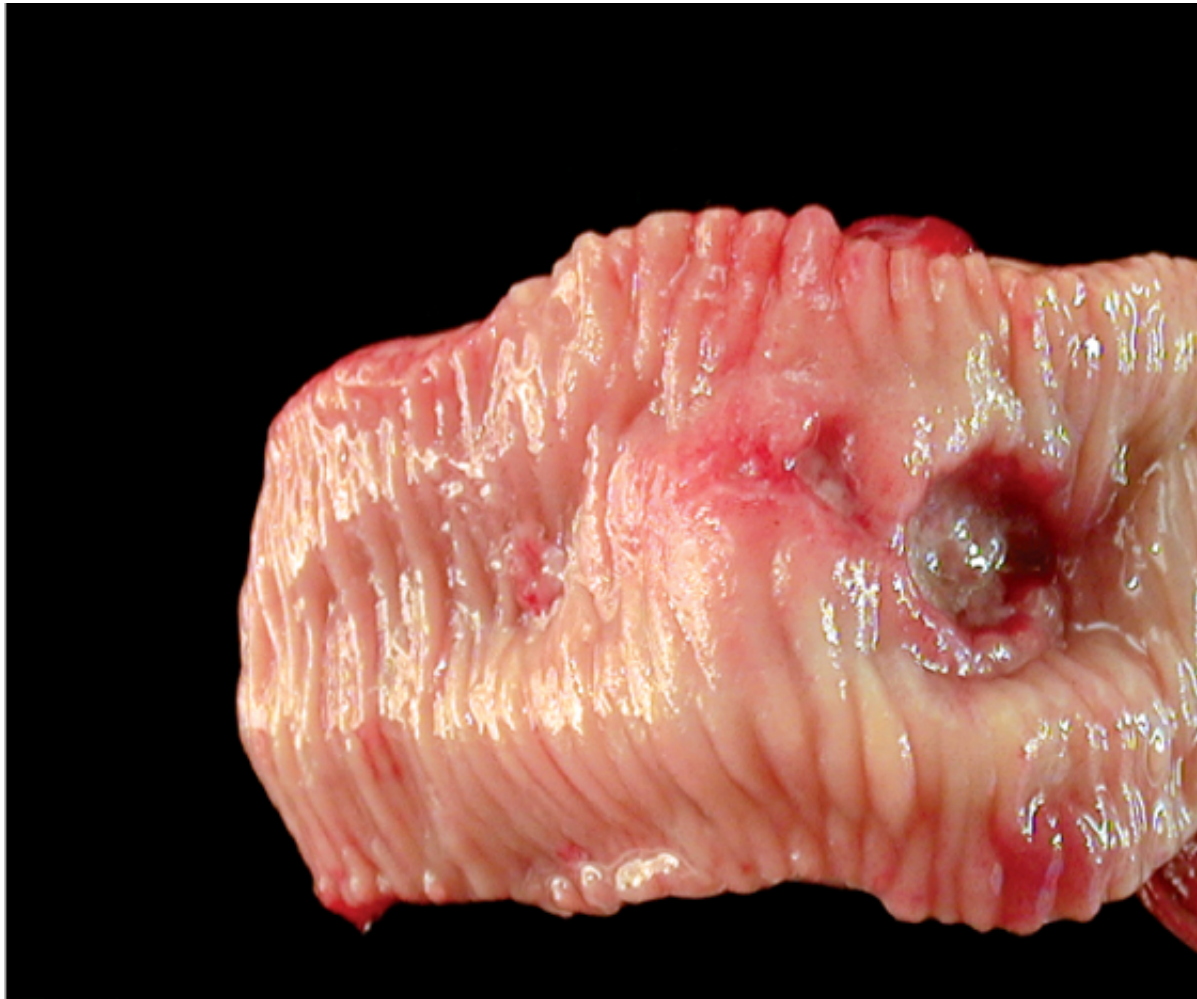
Although *H. pylori* does not invade the tissues, it induces an intense inflammatory and immune response. It stimulates production of proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor- $\alpha$  produced by the mucosal epithelial cells, and it recruits and activates neutrophils. Several bacterial factors are causing epithelial cell injury and induction of inflammation. Epithelial injury is mostly caused by the cytotoxin-associated gene A (*CagA*). This gene is a component of a pathogenicity island of 29 genes, some of which encode pro-inflammatory proteins. In addition, *H. pylori* secretes urease, which forms toxic compounds such as ammonium chloride and monochloramine. The organisms damage surface epithelial cells. Bacterial proteases and phospholipases break down the gastric mucus, thus weakening the first line of mucosal defense. *H. pylori* enhances gastric acid secretion, thus reducing luminal pH in the duodenum. This altered milieu seems to favor gastric epithelium in the first part of the duodenum. Such metaplastic foci provide areas for bacterial colonization. Proteins are immunogenic, and they evoke a robust immune response in the mucosa. Both in chronic gastritis caused by *H. pylori*. The B lymphocytes aggregate to form follicles. The injury is not established, but T-cell-driven activation of B cells may be involved in the pathogenesis of gastric lymphomas, discussed later in this chapter.

Only 10% to 20% of individuals worldwide who are infected with *H. pylori* actually develop peptic ulcer. Some are spared and some are susceptible. Perhaps there are interactions between *H. pylori* and the mucosal defenses in some individuals. Emerging evidence also strongly implicates bacterial factors. Thus, strains producing more severe tissue inflammation, more severe epithelial damage, and higher cytokine production. Recent molecular studies have identified subtle genetic differences between different strains that may influence their pathogenicity. Suffice to say, *pylori* infection and gastric and duodenal ulcers is well established, variability in host-pathogen interaction remains to be deciphered.

NSAIDs are the major cause of peptic ulcer disease in persons who do not have *H. pylori* infection. NSAIDs range from acute erosive gastritis and acute gastric ulceration to peptic ulceration in 1% to 3% of those taking them. Among the most commonly used medications, the magnitude of gastroduodenal toxicity caused by these agents increases with age, higher dose, and prolonged usage. Thus, the elderly and those with rheumatic conditions are at particularly high risk. Suppression of mucosal prostaglandin synthesis by NSAIDs, which reduces hydrochloric acid and reduces bicarbonate and mucin production, is the key to NSAID-induced peptic ulceration. The mucosal barrier that normally prevents acid from reaching the epithelium is weakened. Synthesis of glutathione is reduced. Some NSAIDs can penetrate the gut mucosal cells as well. Whether coexisting *H. pylori* infection and NSAID-induced ulceration is not entirely settled.

Other events may act alone or in concert with *H. pylori* and NSAIDs to promote peptic ulceration.

...these may decrease or increase gastric acid secretion and hence promote peptic ulceration. Excess production of gastric acid from a tumor in individuals with the *Zollinger-Ellison* syndrome causes peptic ulcerations in the stomach, duodenum, and even the jejunum. *Cigarette smoking* impairs mucosal defense and has not been proved to directly cause peptic ulceration, but alcoholic cirrhosis is associated with a higher incidence of peptic ulcer. *Corticosteroids* in high dose and with repeated use promote ulcer formation. There are also complex interactions between psychological stress and peptic ulcer. Although this is now accepted as "common knowledge," the mechanisms of these effects are lacking.



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Figure 15-16 Peptic ulcer of the duodenum. Note that the ulcer is small (2 cm) with a sharply punched-out appearance. The ulcer base is clean (compare with the ulcerated carcinoma in Fig. 15-19). (Courtesy of Dr. Robin F.

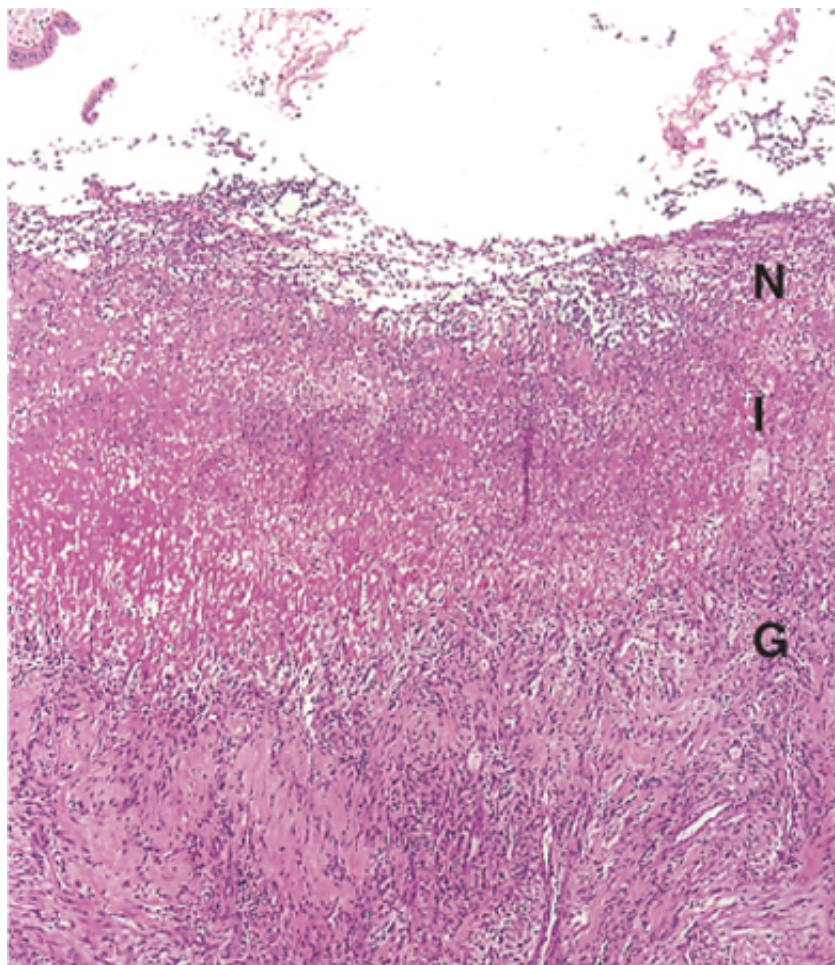
### Morphology

All peptic ulcers, whether gastric or duodenal, have an identical gross and microscopic definition, **they are defects in the mucosa that penetrate at least into the submucosa or the muscularis propria or deeper. Most are round, sharply punched-out craters** (Fig. 15-16); those in the duodenum tend to be smaller, and occasional gastric lesions are larger. Favored sites are the anterior and posterior walls of the first portion of the duodenum and the lesser curvature of the stomach. The location within the stomach is dictated by the extent of the disease. Antral gastritis is most common, and the ulcer is often along the lesser curvature at the junction of the antrum and the inflamed area and the upstream acid-secreting mucosa of the corpus. Occasional ulcers are on the greater curvature or anterior or posterior walls of the stomach, the very same locations as gastric cancers.

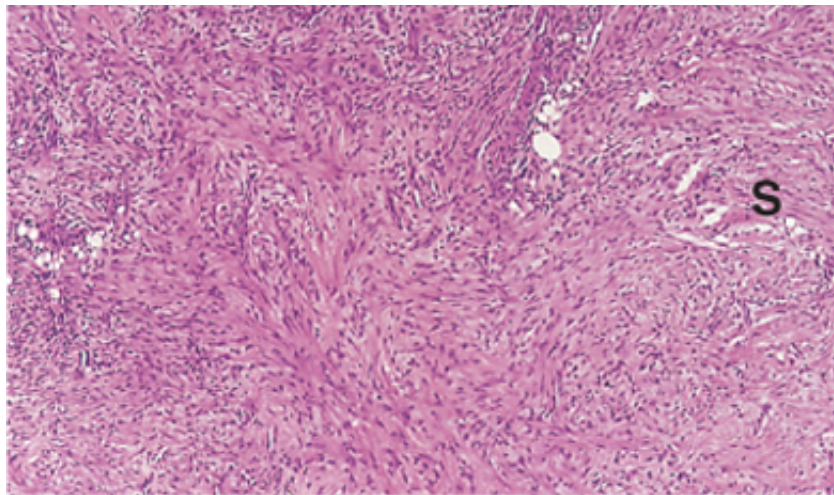
Classically, **the margins of the crater are perpendicular and there is some milk immediately adjacent mucosa, but unlike ulcerated cancers there is no significant beading of the edges.** The surrounding mucosal folds may radiate like wheel spokes. The ulcer crater appears remarkably clean, as a result of peptic digestion of the inflammatory exudate. Infrequently, an eroded artery is visible in the ulcer (usually associated with a histiocytic reaction). If the ulcer crater penetrates through the duodenal or gastric wall, a localized or general perforation may develop. Alternatively, the perforation is sealed by an adjacent structure such as a loop of small intestine or pancreas.

The histologic appearance varies with the activity, chronicity, and degree of healing. Four zones can be distinguished (Fig. 15-17): (1) the base and margins have a thin layer of debris underlain by (2) a zone of active nonspecific inflammatory infiltration with neutrophils, (3) granulation tissue, deep to which is (4) fibrous, collagenous scar tissue. Vessels trapped within the scarred area are characteristic. With healing, granulation tissue is replaced by re-epithelialization from the margins and more or less normal architecture (hence the prolonged healing times). Extensive fibrous scarring is characteristic of chronic ulcers.

Chronic gastritis is extremely common among persons with peptic ulcer disease, and is almost always demonstrable in those persons with gastritis. Similarly, individuals with peptic ulcers do not have gastritis unless there is coexistent *H. pylori* infection. This distinguishes peptic ulcers from acute gastric ulceration (discussed later), because the normal mucosa is generally absent in the latter condition.







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Figure 15-17 Medium-power detail of the base of a nonperforated peptic ulcer, demonstrating the layers of necrosis and scar (S) moving from the luminal surface at the top to the muscle wall at the bottom.

### Clinical Features

Most peptic ulcers cause epigastric pain, often described as gnawing, burning, or boring, but a significant complication such as hemorrhage or perforation. The pain tends to be worse at night and occurs on an empty stomach. Classically, the pain is relieved by alkalis or food, but there are many exceptions. Nausea and vomiting, and significant weight loss (raising the specter of some hidden malignancy) are additional manifestations.

*Bleeding is the chief complication*, occurring in as many as one-third of patients, and may be life-threatening. It occurs in about 5% of patients but accounts for two-thirds of deaths from this disease in the United States. Obstruction occurs in about 5% of patients, generally from ulcers in the pyloric channel. Malignant transformation occurs in about 2% of patients, generally from ulcers in the pyloric channel. In the latter event, it is often difficult to exclude the possibility that carcinoma was present from the onset.

*Peptic ulcers are notoriously chronic, recurrent lesions*; they more often impair the quality of life than cause death. Modern medical therapies (including antibiotics active against *H. pylori*, proton pump inhibitors, and hydrogen receptor antagonists) can be helped if not cured, and they usually escape the surgeon's knife.

### Acute Gastric Ulceration

Focal, acutely developing gastric mucosal defects that may appear after severe physiologic stress are many lesions located mainly in the stomach and occasionally in the duodenum. Stress ulcers occur in various conditions:

- Severe trauma, including major surgical procedures, sepsis, shock, or grave illness of any kind.
- Drugs, particularly NSAIDs and corticosteroids.
- Extensive burns (these ulcers are known as Curler ulcers).
- Injury to the central nervous system or an intracerebral hemorrhage (called Cushing ulcers).

The pathogenesis of these lesions is uncertain and may vary with the setting. NSAID-induced ulcers are thought to result from inhibition of prostaglandin production. The systemic acidosis that can accompany severe trauma and burns may contribute to the intracellular pH of mucosal cells already rendered hypoxic by impaired mucosal blood flow. Withdrawal of vagal nuclei by increased intracranial pressure may cause gastric acid hypersecretion, which is common in Cushing ulcers.







lamina propria with intestinal metaplasia and frequently, proliferation of lymphocytes, a precursor of peptic ulcer and carcinoma. *Acute gastritis*: acute mucosal inflammation associated with use of NSAIDs, alcohol, heavy smoking, and various systemic diseases. *Ulcer*: breach in the epithelium caused most commonly by *H. pylori* infection and gastric acid and enzymes (pepsin), or less frequently by use of NSAIDs; *H. pylori* infection causes a chronic reaction and damages epithelial cells; typically, sharply demarcated mucosal ulcer with necrosis, acute inflammation, granulation tissue, and scarring; manifested by abdominal pain, commonly, rupture. *Stress ulcers (acute gastric ulcers)*: associated with severe burns, trauma or hemorrhage; usually small, multiple, hemorrhagic ulcers that are



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## GASTRIC TUMORS

As with the remainder of the gastrointestinal tract, tumors arising from the mucosa predominate and tumors are classified into polyps and carcinoma.

### Gastric Polyps

*The term polyp is applied to any nodule or mass that projects above the level of the surrounding mucosa. A leiomyoma arising in the wall of the stomach may protrude from under the mucosa to produce an ulcer. The use of the term polyp in the gastrointestinal tract is generally restricted to mass lesions arising in the mucosa. Polyps are uncommon and are found in about 0.4% of adult autopsies, as compared with colonic polyps, which are found in 10% to 20% of persons. In the stomach, these lesions are most frequently (1) hyperplastic polyps (80% to 85%), (2) adenomatous polyps (~5%), and (3) fundic gland polyps (~5%). All three types arise in the setting of chronic gastritis and so are seen in patients with chronic gastritis. Hyperplastic and fundic gland polyps are essentially innocuous. In contrast, there is a definite risk of adenocarcinoma, which increases with polyp size. Because the different types of gastric polyps cannot be distinguished by endoscopy, histologic examination is mandatory.*

### Morphology

Hyperplastic polyps arise from an exuberant reparative response to chronic mucositis and are composed of a hyperplastic mucosal epithelium and an inflamed edematous stroma. Fundic gland polyps are small collections of dilated corpus-type glands and are hamartomas. On the other hand, the less common adenomas contain dysplastic epithelium and, to be described later, adenomas are true neoplasms.

### Gastric Carcinoma

Among the malignant tumors that occur in the stomach, carcinoma is overwhelmingly the most important (95%). Next in order of frequency are lymphomas (4%), carcinoids (3%), and stromal tumors (2%). This section focuses on gastric carcinomas, with only a brief mention of the other types. Gastrointestinal stromal tumors are discussed later in this chapter, after the presentation of intestinal tumors.

#### *Epidemiology and Classification*

Gastric carcinoma is the second leading cause of cancer-related deaths in the world, with a widely variable incidence. Japan and South Korea have the highest incidence (eight to nine times higher than in the United States); in many other countries, such as China and Chile and Costa Rica, is also high. Nevertheless, in recent years there has been a decline in the overall incidence and the mortality of gastric cancer. Yet it remains the leading killer with a discouraging 5-year survival rate, which remains at less than 20%. It is responsible for approximately 10% of all cancer deaths in the United States.

Gastric cancers show two morphologic types, called *intestinal* and *diffuse*. The *intestinal type* is the type that has undergone intestinal metaplasia in the setting of chronic gastritis. This pattern of cancer is the more common type in high-risk populations. The *diffuse variant* is thought to arise de novo and is not associated with chronic gastritis, and tends to be poorly differentiated. Whereas the intestinal-type cancer increases with age with a 2 : 1 male predominance, the diffuse carcinoma occurs at an earlier age with female predominance. *Intestinal-type carcinoma has progressively diminished in the United States. By contrast, the incidence of diffuse-type carcinoma has significantly changed in the past 60 years and now constitutes approximately half of gastric carcinomas. Intestinal and diffuse forms of gastric carcinomas can be considered as distinct entities, although their clinical behavior is often similar.*

### ***Etiology and Pathogenesis***

#### *Intestinal-Type Adenocarcinoma*

**Table 15-5. Risk Factors for Gastric Carcinoma**

<b>Intestinal-Type Adenocarcinoma</b>
Chronic gastritis with intestinal metaplasia
Infection with <i>Helicobacter pylori</i>
Nitrites derived from nitrates (found in food and drinking water, and used as preservatives in prepared meats, nitrosamines and nitrosamides)
Diets containing foods that may generate nitrites (smoked foods, pickled vegetables and excessive salt intake)
Decreased intake of fresh vegetables and fruits (antioxidants present in these foods may inhibit nitrosation)
Partial gastrectomy
Pernicious anemia
<b>Diffuse Carcinoma</b>
Risk factors undefined, except for a rare inherited mutation of E-cadherin
Infection with <i>H. pylori</i> and chronic gastritis often absent

Several major variables are thought to affect the genesis of this form of cancer (Table 15-5). The relative importance of these factors is changing. For example, dietary influences have changed drastically in refrigeration worldwide, markedly decreasing the need for food preservation by nitrates, smoking, and gastric infection. Gastritis associated with *H. pylori* infection constitutes a major risk factor for gastric carcinoma. The inflammation is usually limited to the gastric pylorus and antrum. Gastritis is generally accompanied by intestinal metaplasia, which are ultimately followed by dysplasia and cancer. The mechanisms of neoplastic transformation are not fully understood. Chronic inflammation induced by *H. pylori* may release reactive oxygen species, which eventually lead to an imbalance between cell proliferation and apoptosis, particularly in areas of tissue repair. Notably, duodenal ulcers are largely protected from developing gastric cancer. Amplification of *HER-2/NEU* is present in 20% to 30% of cases and is absent in diffuse carcinoma.

#### *Diffuse Adenocarcinoma*

The risk factors for this type of cancer remain undefined (Table 15-5), and precursor lesions have been identified. *E-cadherin*, which are not detectable in intestinal-type cancers, are present in 50% of diffuse cancer. The hereditary form of diffuse gastric cancer, caused by germ-line mutation in *E-cadherin*. Mutations in the *ras* oncogene, *erbB-2* growth factor receptor family, and increased expression of metalloproteinases are present in about 50% of intestinal-type carcinomas.

#### **Morphology**

The location of gastric carcinomas within the stomach is as follows: pylorus and antrum account for 25%; and the remainder in the body and fundus. The lesser curvature is involved in 12% of cases, and the greater curvature in 12%. **Thus, a favored location is the lesser curvature of the stomach.** Though less frequent, an ulcerative lesion on the greater curvature is more likely to be benign.

Gastric carcinoma is classified on the basis of depth of invasion, macroscopic growth pattern, and histologic subtype. The morphologic feature having the greatest impact on clinical outcome is the depth of invasion. **Early gastric carcinoma is defined as a lesion confined to the mucosa and submucosa, with or without the presence or absence of perigastric lymph node metastases. Advanced gastric carcinoma is defined as a neoplasm that has extended below the submucosa into the muscular wall and beyond.** Gastric mucosal **dysplasia** is the presumed precursor lesion of early gastric carcinoma. It in turn progresses to "advanced" lesions.

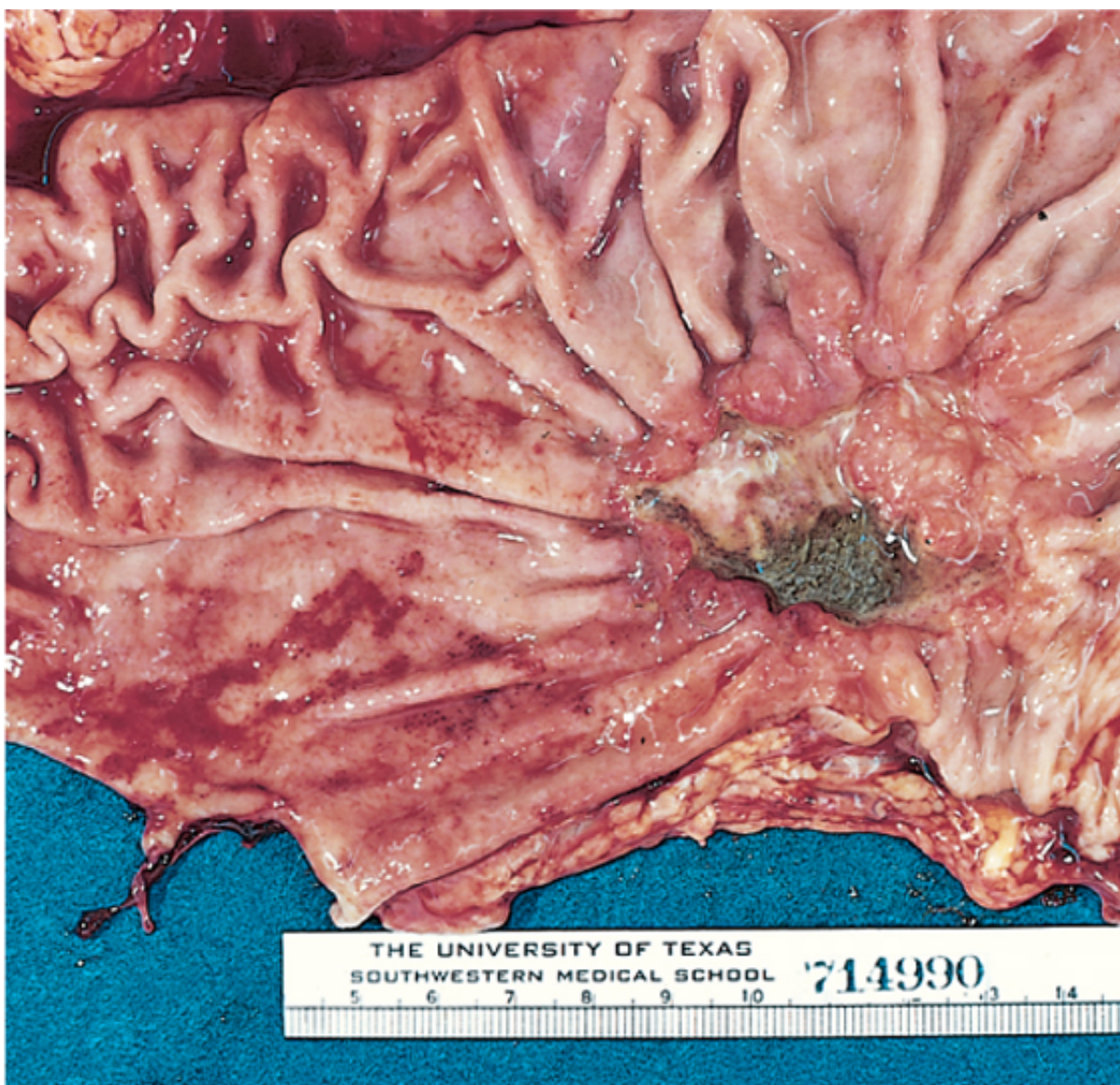
The three macroscopic growth patterns of gastric carcinoma, which may be evident at early or advanced stages, are (1) **exophytic**, with protrusion of a tumor mass into the lumen of the stomach; (2) **infiltrative**, in which there is no obvious tumor mass within the mucosa; and (3) **excavated**, with the formation of an erosive crater is present in the wall of the stomach. Exophytic tumors may contain ulceration. Infiltrative malignancy presents only as regional effacement of the normal mucosal folds. Excavated cancers may mimic, in size and appearance, chronic peptic ulcers, although the margins are irregular and the base is indurated.



cases show heaped-up margins (Fig. 15-19). Uncommonly, a broad region of the stomach, is extensively infiltrated by malignancy. The rigid and thickened stomach, or **linitis plastica**; metastatic carcinoma from the breast and lung may grow

As mentioned earlier, histologic appearances of gastric cancer are best classified into the diffuse type (Fig. 15-20). The **intestinal variant** is composed of malignant cells forming glands resembling those of colonic adenocarcinoma. The **diffuse variant** is composed of mucous cells that generally do not form glands but rather permeate the mucosa as individual "**signet-ring**" cells or small clusters in an "infiltrative" growth pattern.

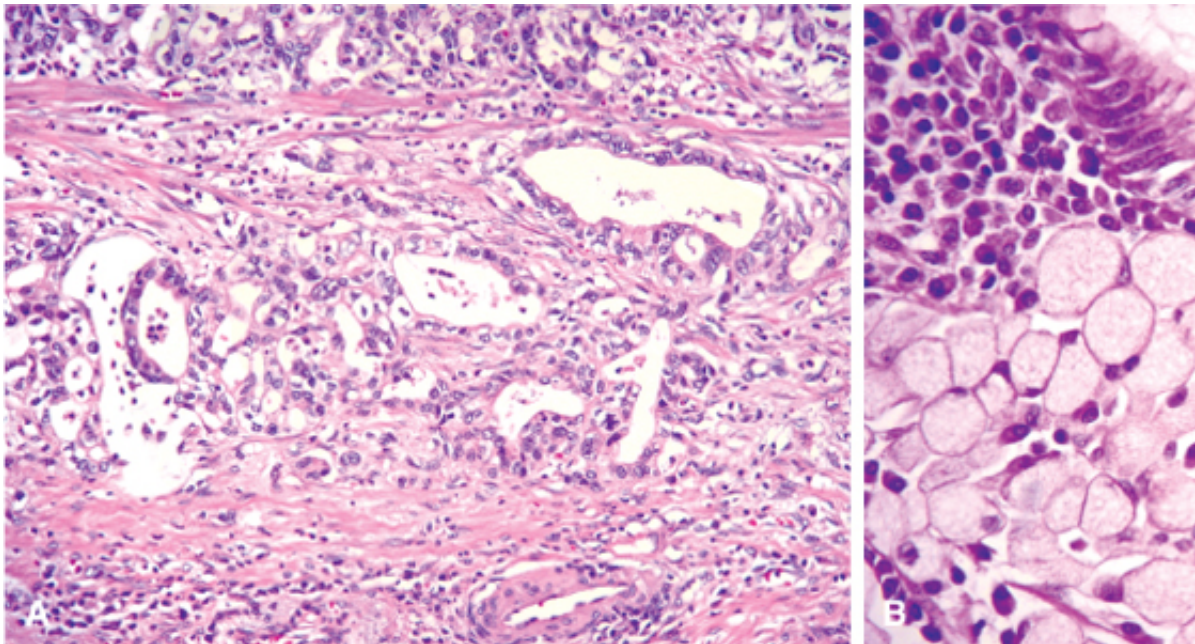
Whatever the histologic variant, all gastric carcinomas eventually penetrate the wall and spread to regional and more distant lymph nodes, and metastasize widely. For observation of lymph node metastasis may sometimes involve a supraclavicular lymph node (Virchow's node). A somewhat unusual mode of intraperitoneal spread in females is to both the ovaries called **Krukenberg tumor** (Chapter 19).



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Figure 15-19 Ulcerative gastric carcinoma. The ulcer is large with irregular, heaped-up margins. There is extensive gray area in the deepest portion. Compare with the benign peptic ulcer in Fig

### Clinical Features

Both intestinal-type and diffuse gastric carcinoma are generally asymptomatic and can be discovered on endoscopic examinations in persons at high risk. Advanced carcinoma also may be asymptomatic, but it often causes abdominal discomfort or weight loss. Uncommonly, these neoplasms cause dysphagia when they are located in the esophagus or when they arise in the pyloric canal. The only hope for cure is early detection and surgical removal. The most important prognostic indicator is stage of the tumor at the time of resection.



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Figure 15-20 Gastric cancer. **A**, H&E stain demonstrating intestinal type of gastric carcinoma with gland formation in the wall of the stomach. **B**, Diffuse type of gastric carcinoma with signet-ring tumor cells.

### SUMMARY

**Gastric Tumors** More than 90% of gastric tumors are carcinomas; lymphomas are relatively infrequent. The two main types of gastric adenocarcinoma are intestinal and diffuse types; macroscopic patterns of both types may be exophytic, flat or ulcerating. *Intestinal type of adenocarcinoma* is associated with chronic gastritis, with gastric atrophy and intestinal metaplasia; composed of malignant glands. *Diffuse type of adenocarcinoma* is not associated with *H. pylori* infection; composed of mucous cells (signet ring cells) that permeate the mucosa without forming glands.





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## SMALL AND LARGE INTESTINES

Many conditions, such as infections, inflammatory diseases, and tumors, affect both the small and large intestines. These two organs are therefore considered together. Collectively, disorders of the intestines account for a large portion of human disease.



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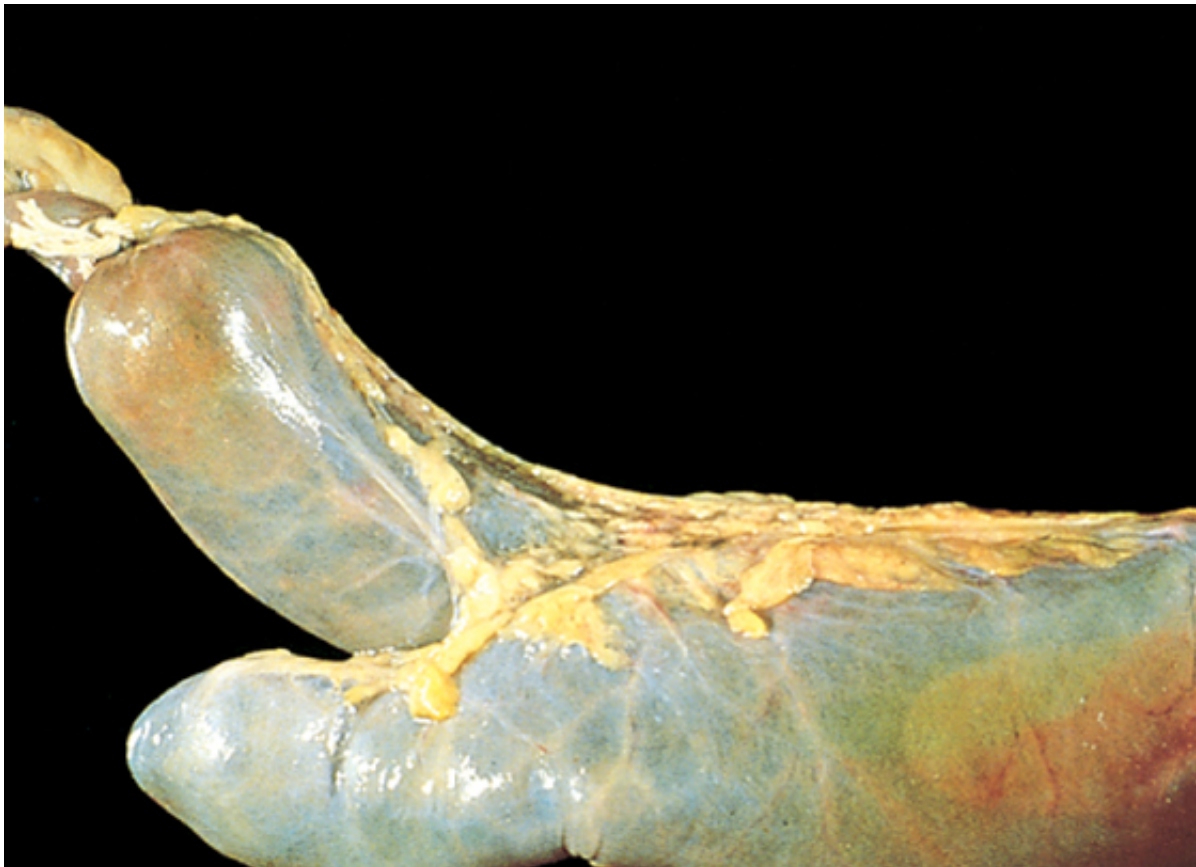


## DEVELOPMENTAL ANOMALIES

These defects are uncommon but sometimes result in serious clinical disease.

*Atresia*, the complete failure of development of the intestinal lumen, and *stenosis*, narrowing or obstruction, may affect any segment of the small intestine, but duodenal atresia is the most common form of well-formed saccular to tubular cystic structures, which may or may not communicate with the intestine. *Meckel diverticulum* is the most common and innocuous of the anomalies. It results from the persistence of the omphalomesenteric duct, leaving a persistent blind-ended tubular protrusion as long as 5 cm, which is variable, sometimes approximating that of the small intestine itself. Such diverticula are usually located within 100 cm of the ileocecal valve, and are composed of all layers of the normal small intestine. They generally do not cause problems, but they permit bacterial overgrowth that depletes vitamin B<sub>12</sub>, producing a syndrome similar to pernicious anemia. Sometimes, heterotopic gastric rests are found in a Meckel diverticulum, and in about half of the cases there are heterotopic gastric rests. Peptic ulceration in the adjacent intestinal mucosa sometimes is responsible for mysterious abdominal pain resembling acute appendicitis. *Omphalocele* is a congenital defect of the periumbilical abdominal wall, into which the intestines herniate. In *gastroschisis*, extrusion of the intestinal loops through a defect in the abdominal wall. In *malrotation*, abnormal rotation of the developing bowel can prevent the intestine from assuming its normal abdominal positions. The cecum, for example, may be found anywhere in the abdomen, instead of its normal position in the right lower quadrant. The large intestine is predisposed to clinical syndromes may arise when appendicitis presents as left upper quadrant pain. *Hirschsprung disease* is a congenital megacolon. This condition is discussed separately.

### Hirschsprung Disease: Congenital Megacolon







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Figure 15-21 Meckel diverticulum. The blind pouch is located on the antimesenteric side

Distention of the colon to greater than 6 or 7 cm in diameter (megacolon) occurs as a congenital disease (congenital megacolon) results when, during development, the migration of neural crest cells arrests at some point before reaching the anus. Hence, an *aganglionic* segment is formed that lacks Auerbach myenteric plexuses. This causes functional obstruction and progressive distention of the colon. Ganglia are absent from the muscle wall and submucosa of the constricted segment but may be present in the distended segment.

Genetically, Hirschsprung disease is heterogeneous, and several different defects that lead to the disease. Approximately 50% of familial cases result from mutations in *RET* genes and RET ligands, because RET provides direction to migrating neural crest cells. Mutations in endothelin 3 and endothelin receptors. Hirschsprung disease occurs in approximately 1 in 5000 live births and predominates in males in a ratio of 4:1. It is much more frequent in those with other congenital anomalies, such as ventricular septal defect, and Meckel diverticulum.

### Morphology

**The critical lesion in Hirschsprung disease is the lack of ganglion cells, and the absence of the myenteric plexus in the wall and submucosa of the affected segment.** The affected segment is not distended. The segment proximal to the constricted segment undergoes dilation. Thus, when only the distal colon is involved, the remainder of the colon becomes massively distended, sometimes achieving a diameter of 10 cm or more. The colonic wall may be thinned by distention or in some cases is thickened by compensatory hypertrophy. The mucosal lining of the distended portion may be intact or have shallow, so-called *saucer-shaped* ulcers caused by impacted, inspissated feces.

### Clinical Features

In most cases a delay occurs in the initial passage of meconium, which is followed by vomiting in the neonatal period. If only a segment of the rectum alone is involved, the obstruction may not be complete and may not produce the form of alternating periods of obstruction and passage of diarrheal stools. The principal threat to life is dehydration and electrolyte disturbances. More rarely, the distended colon perforates, usually in the thin-walled segment. The diagnosis is established by documenting the absence of ganglion cells in the *nondistended* bowel segment.

*Acquired megacolon* may result from (1) Chagas disease, in which the trypanosomes directly invade the myenteric plexuses, (2) organic obstruction of the bowel by a neoplasm or inflammatory stricture, (3) toxic megacolon in Crohn disease (discussed later), or (4) a functional psychosomatic disorder. Except for the trypanosome, inflammatory involvement of the ganglia is evident, the remaining forms of megacolon are not associated with a lack of ganglia.

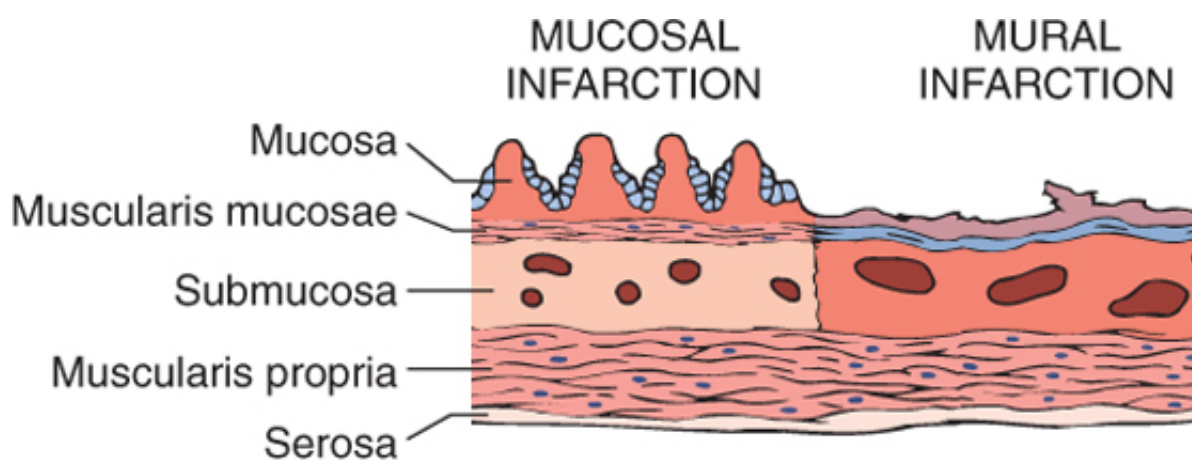




## VASCULAR DISORDERS

### Ischemic Bowel Disease

Ischemic lesions may be restricted to the small or large intestine or may affect both, depending on the site of occlusion. Acute occlusion of one of the three major supply trunks of the intestines—celiac, superior, and inferior mesenteric—results in infarction of extensive segments of intestine. However, insidious loss of one vessel may be without obvious clinical consequences. Lesions within the end-arteries that penetrate the gut wall produce small, focal infarcts. In Figure 15-22, the severity of injury ranges from *transmural infarction* of the gut, involving all viscera, to *mucosal infarction*, if the lesion extends no



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Figure 15-22 Acute ischemic bowel disease. Note the three levels of severity, represented by the extent of hemorrhage and necrosis.

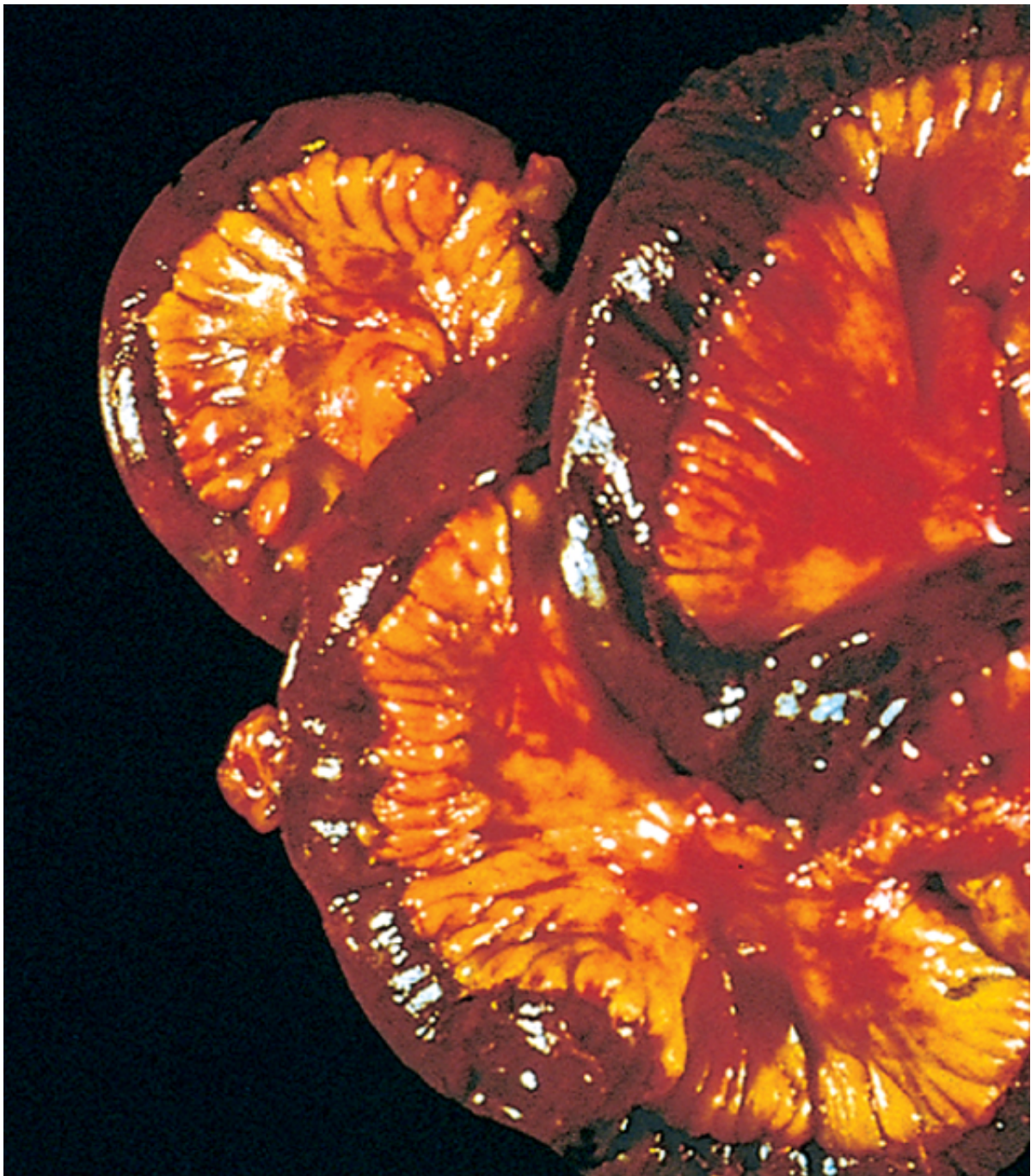
Almost always, *transmural infarction* is caused by acute occlusion of a major mesenteric artery. Mesenteric artery occlusion results from either physiologic hypoperfusion or more localized anatomic defects, and may be acute or chronic. Thrombosis or embolism is a less frequent cause of vascular compromise. The predisposing conditions for all three

**Arterial thrombosis:** severe atherosclerosis (usually at the origin of the mesenteric vessel), angiographic procedures, aortic reconstructive surgery, surgical accidents, hypercoagulable states.  
**Embolism:** cardiac vegetations (as with endocarditis, or myocardial infarction with mural thrombi), aortic atheroembolism.  
**Venous thrombosis:** hypercoagulable states induced, for example, by oral contraceptives, pregnancy, dehydration, intraperitoneal sepsis, the postoperative state, vascular-invasive neoplasms (pancreatic cancer), cirrhosis, and abdominal trauma.  
**Nonocclusive ischemia:** cardiac failure, shock, dehydration.  
**Miscellaneous:** radiation injury, volvulus, stricture, and internal hernia.

### Morphology

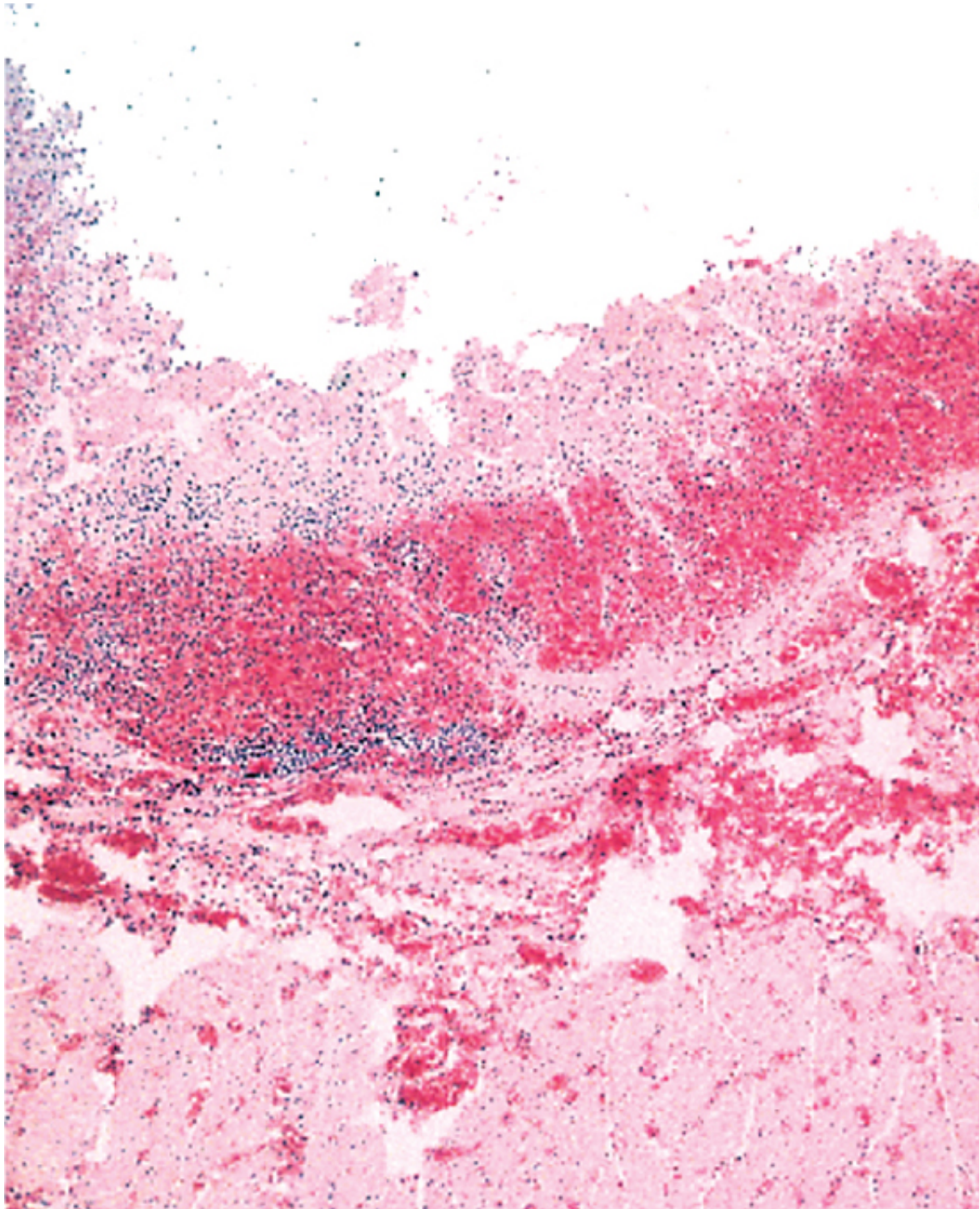
**Transmural intestinal infarction** may involve a short or long segment, depending on the site of occlusion and the patency of the anastomotic supply. Whether the occlusion is arterial or venous, the infarct always has a dark red hemorrhagic appearance because of reflow of blood into the infarcted area (Figure 23). The ischemic injury usually begins in the mucosa and extends outward; within 24 hours, a thin, fibrinous exudate covers the serosa. With arterial occlusion the demarcation from normal bowel is fairly sharply defined, but with venous occlusion the margins are less distinct. Histologically, the infarct shows typical of ischemic damage with marked edema, interstitial hemorrhage, necrosis, and inflammation. Within 24 hours intestinal bacteria produce outright gangrene and sometimes perforation of the bowel.

**Mural and mucosal infarctions** are recognized by multi-focal lesions interspersed. Location depends in part on the extent of preexisting atherosclerotic narrowing of the mesenteric arteries. Lesions can be scattered over large regions of the small or large intestines. Affected foci may be seen from the serosal surface, because by definition the ischemia does not affect the entire bowel wall. When the bowel is opened, hemorrhagic edematous thickening of the mucosa, sometimes with ulcerations, is seen. Histologic features are those of acute injury: edema, hemorrhage, and necrosis of the affected tissue layers (Fig. 15-24). Inflammation develops at the margins of the infarct, with an inflammatory fibrin-containing exudate (**pseudomembrane**), usually secondary to the infarction. This may coat the affected mucosa. Alternatively, **chronic vascular insufficiency** may develop as a long-standing inflammatory and ulcerative condition, mimicking idiopathic inflammatory bowel disease.





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Figure 15-23 Infarcted small bowel, secondary to acute thrombotic occlusion of the supe



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Figure 15-24 Mucosal infarction of the small bowel. The mucosa is hemorrhagic, and there is no epithelial layer

### *Clinical Features*

Ischemic bowel injury is most common in the later years of life. With the transmural lesions, there



Ischemic bowel injury is most common in the later years of life. With the transmural lesions, there is often a disproportionate relationship between the pain and the physical signs. Sometimes the pain is accompanied by bloody diarrhea. Sudden collapse with mesenteric embolism is more common than with arterial or venous thrombosis. Because this condition can collapse within hours, the diagnosis must be made promptly, and making it requires a high index of suspicion (e.g., recent major abdominal surgery, recent myocardial infarction, atrial fibrillation, or manifest vegetative endocarditis). The mortality rate with infarction of the bowel approaches 90%, largely because of the rapid onset of symptoms and perforation caused by gangrene is so small.

By contrast, mural and mucosal ischemia may appear only as unexplained abdominal distention accompanied by the gradual onset of abdominal pain or discomfort. Suspicion is raised if the individual has risk factors favor acute hypoperfusion of the bowel, such as an episode of cardiac decompensation or shock. These lesions are themselves fatal, and, indeed, if the cause or causes of hypoperfusion can be corrected, the lesions may heal.

### Angiodysplasia

Tortuous dilations of submucosal and mucosal blood vessels are seen most often in the cecum or ascending colon in the later decade of life. They are prone to rupture and bleed into the lumen. *Such lesions account for 20% of the causes of chronic blood loss from the gastrointestinal tract.* The hemorrhage may be chronic and intermittent and only cause severe anemia, but rarely it is associated with shock.

These lesions sometimes are part of a systemic disorder such as hereditary hemorrhagic telangiectasia or Ehler-Danlos syndrome, sometimes called the CREST syndrome (Chapter 5). Most often, they are isolated lesions that develop over decades as the result of mechanical influences operative in the colonic wall. As penetrating veins are subject to intermittent occlusion during peristaltic contractions, but the thicker walled arteries remain patent, the result is distention and ectasia.

### Hemorrhoids

Hemorrhoids are variceal dilations of the anal and perianal submucosal venous plexuses. They are most common in the setting of persistently elevated venous pressure within the hemorrhoidal plexus. Common precipitating factors are chronic constipation and the venous stasis of pregnancy in younger women. More serious proximal lesions. They may become thrombosed, particularly when subject to trauma from straining at stool and then become trapped by the compressive forces of the anal sphincter, resulting in extremely painful, edematous hemorrhagic enlargement or strangulation.

Varicosities in the superior and middle hemorrhoidal veins appear above the anorectal line and are called *internal hemorrhoids*. Those that appear below the anorectal line represent dilations of the inferior hemorrhoidal veins and are called *external hemorrhoids*. Both are thin-walled, dilated vessels that commonly bleed, sometimes causing significant blood loss. They may become thrombosed, particularly when subject to trauma from straining at stool and then become trapped by the compressive forces of the anal sphincter, resulting in extremely painful, edematous hemorrhagic enlargement or strangulation.





## COLONIC DIVERTICULOSIS

*A diverticulum is a blind pouch that communicates with the lumen of the gut.* Congenital diverticula have all three layers of the bowel wall (mucosa, submucosa, and most notably the muscularis propria) and are distinctly uncommon. The prototype is *Meckel diverticulum*, described above.

Virtually all other diverticula are acquired and either lack or have an attenuated muscularis propria. *Acquired diverticula may occur anywhere in the alimentary tract, but by far the most common location is the colon*, giving rise to *diverticular disease* of the colon, also called *diverticulosis*. The colon is unique in that the outer longitudinal muscle coat is not complete but is gathered into three equidistant bands (the taeniae coli). Focal defects in the muscle wall are created where nerves and arterial vasa recta penetrate the inner circular muscle coat alongside the taeniae. The connective tissue sheaths accompanying these penetrating vessels provide potential sites for herniations.

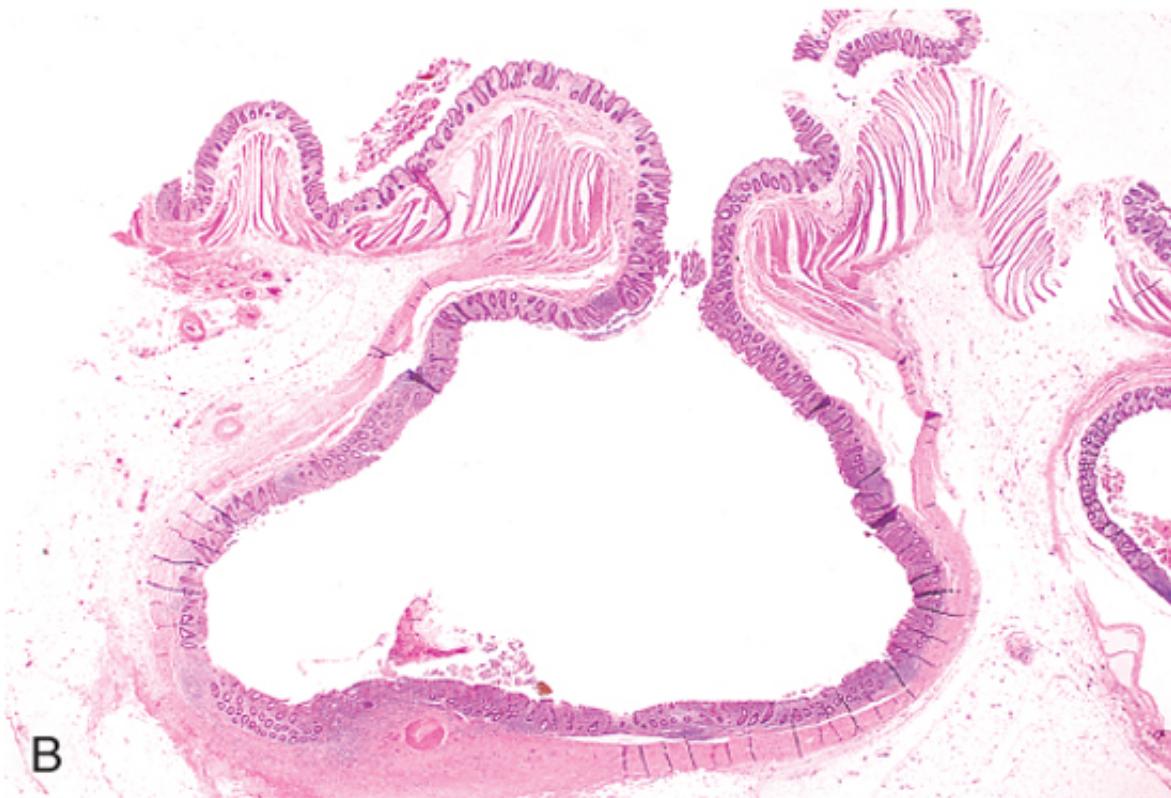
Colonic diverticulosis is relatively infrequent in native populations of non-Western countries. Although unusual in Western adults younger than 30 years of age, in those older than the age of 60 the prevalence approaches 50%. This high prevalence is attributed to the consumption of a refined, low-fiber diet in Western societies, resulting in reduced stool bulk with increased difficulty in passage of intestinal contents. Exaggerated spastic contractions of the colon isolate segments of the colon (segmentation) in which the intraluminal pressure becomes markedly elevated, with consequent herniation of the bowel wall through the anatomic points of weakness. Thus, *two* influences are thought to be important in the genesis of diverticular protrusions: (1) *exaggerated peristaltic contractions* with abnormal elevation of intraluminal pressure and (2) *focal defects* peculiar to the normal muscular colonic wall.

### Morphology

Most colonic diverticula are **small, flasklike or spherical outpouchings, usually 0.5 to 1 cm in diameter** (Fig. 15-25A). They are located in the sigmoid colon in approximately 95% of patients. Infrequently, more proximal levels and sometimes the entire colon are affected. Isolated cecal diverticula also occur. The exaggerated peristalsis often induces muscular hypertrophy in affected segments, with unusually prominent taenia coli and circular muscle bundles. Most diverticula penetrate between the bundles of circular muscle fibers adjacent to the mesenteric and lateral taeniae at sites of penetrating blood vessels. They frequently dissect into the appendices epiploicae and therefore may be inapparent on casual external inspection.

In the uninflamed state the walls are usually very thin, made up largely of mucosa and submucosa enclosed within fat or an intact peritoneal covering (Fig. 15-25B). Inflammatory changes may supervene to produce both diverticulitis and peridiverticulitis. Perforation may lead to localized peritonitis or abscess formation. When many closely adjacent diverticula become inflamed, the bowel wall may be encased by fibrous tissue, with narrowing of the lumen producing a remarkable resemblance to a cancerous stricture.

### Clinical Features



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 Figure 15-25 Diverticulosis. **A**, Section through the sigmoid colon showing multiple saclike diverticula protruding through the muscle wall into the mesentery. The muscularis between the diverticular protrusions is markedly thickened. **B**, Low-power micrograph of diverticulum of the colon showing protrusion of mucosa and submucosa through the muscle wall. A dilated blood vessel at the base of the diverticulum was a source of bleeding; some blood clot is present within the diverticular lumen.

In most persons, diverticular disease is asymptomatic and is discovered only at autopsy or by chance during a laparoscopy or barium enema for some other problem. In only about a fifth of the cases does intermittent cramping or sometimes continuous left-sided lower quadrant

discomfort appear, with a sensation of never being able to completely empty the rectum. Superimposed diverticulitis accentuates the symptoms and produces left lower quadrant tenderness and fever. Other, less common complications include minimal chronic intermittent bleeding or, rarely, brisk hemorrhage, perforation with pericolic abscess, or fistula formation.

The treatment of this condition merits brief mention, because it bears on its pathogenesis. A high-fiber diet is recommended on the theory that the increased stool bulk reduces the exaggerated peristalsis. Whether a high-fiber diet prevents disease progression or protects against superimposed diverticulitis is unclear, but the diet itself is a source of discomfort.







## BOWEL OBSTRUCTION

Although any part of the gut may be involved, because of its narrow lumen, the small bowel is most commonly involved. Hernias, intestinal adhesions, intussusception, and volvulus-account for at least 80% of the cases

**Table 15-6. Major Causes of Intestinal Obstruction**

<b>Mechanical Obstruction</b>
Hernias, internal or external
Adhesions
Intussusception
Volvulus
<b>Other Less Frequent Conditions</b>
Tumors
Inflammatory strictures
Obstructive gallstones, fecaliths, foreign bodies
Congenital stricture, atresias
Congenital bands
Meconium in cystic fibrosis
Imperforate anus

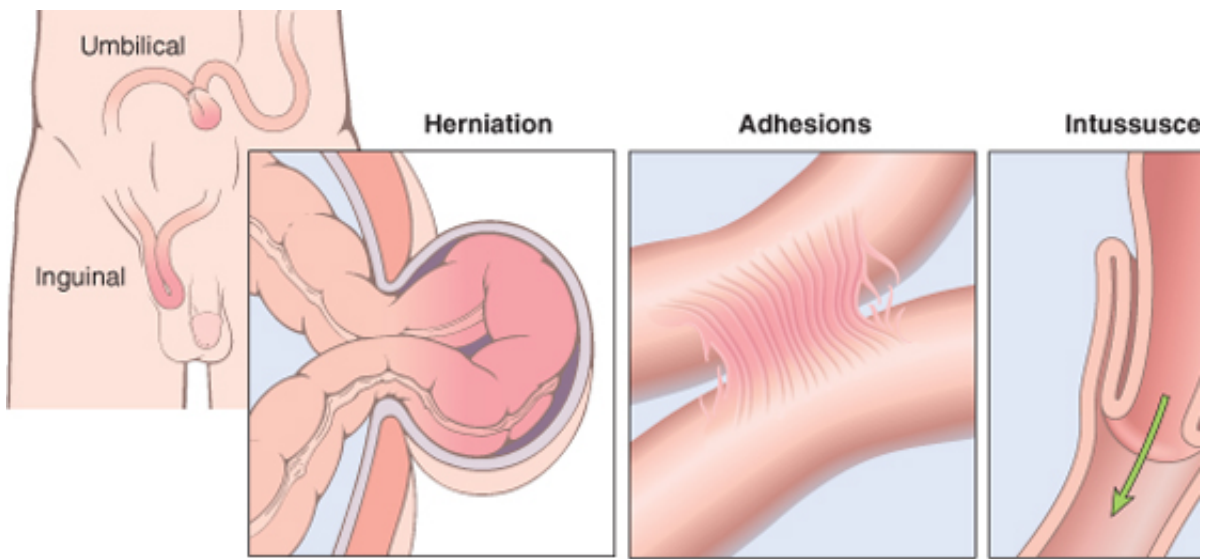
*Hernias*, a weakness or defect in the wall of the peritoneal cavity, may permit protrusion of a pouch called a *hernial sac*. The usual sites of weakness are anteriorly at the inguinal and femoral canals. Rarely, retroperitoneal hernias may occur, chiefly about the ligament of Treitz. *Hernias are of common occurrence and frequently intrude and become trapped in them (external herniation)*. This is particularly true with large orifices and large sacs. The most frequent intruders are small bowel loops, but portions of omentum may also be trapped. Pressure at the neck of the pouch may impair venous drainage of the trapped viscus. The bulk of the herniated loop, leading to permanent trapping (*incarceration*). Further compromise of its blood supply leads to infarction of the trapped segment (*strangulation*).

Surgical procedures, infection, and even endometriosis often cause localized or general peritoneal *adhesions* may develop between bowel segments or the abdominal wall and the operative site. The loops through which the intestines may slide and become trapped (*internal herniation*). The sequelae are similar to those of external hernias.

*Intussusception* denotes telescoping of a proximal segment of bowel into the immediately distal segment. It sometimes occurs without apparent anatomic basis, perhaps related to excessive peristaltic activity. It points to an intraluminal mass (e.g., tumor) that becomes trapped by a peristaltic wave and pulls in the distal segment. Not only does intestinal obstruction ensue, but the vascular supply may be so compromised that the trapped segment becomes necrotic.

*Volvulus* refers to twisting of a loop of bowel or other structure (e.g., ovary) about its base of attachment and sometimes the arterial supply as well. Volvulus affects the small bowel most often and rarely the large bowel. Obstruction and infarction may follow.





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 Figure 15-26 The four major causes of intestinal obstruction: (1) herniation of a segment in the umbilical or inguinal region, (2) adhesions, (3) intussusception, (4) volvulus.





## ENTEROCOLITIS (DIARRHEAL DISEASES)

Diarrheal diseases of the bowel make up a veritable Augean stable of entities (as his fifth labor, H King Augeas, which contained 3000 cattle and had not been swept for 30 years). Many are cause the setting of malabsorptive disorders and idiopathic inflammatory bowel disease.

Although a precise definition of diarrhea is elusive, an increase in stool mass, stool frequency, or : most persons. For many individuals, this consists of daily stool production in excess of 250 gm, or 14 L/day of fluid may be lost in severe cases of diarrhea, equivalent to the circulating blood volume urgency, perianal discomfort, and incontinence. Low-volume, painful, bloody diarrhea is known as

We first list the major types of diarrheal diseases and then discuss infectious enterocolitis and ma bowel disease is presented in a subsequent section.

The major types of diarrheal diseases are:

*Secretory diarrhea*: net intestinal fluid secretion that is isotonic with plasma and persists du osmotic forces exerted by luminal solutes that abate with fasting*Exudative diarrhea*: output fasting; stools are frequent but may be small or large volume*Malabsorption diarrhea*: output increased osmolarity resulting from unabsorbed nutrients and excess fat (steatorrhea); it u: *diarrhea*: highly variable features regarding stool output, volume, and consistency; other fo

The major causes of each of these types of diarrhea are presented in [Table 15-7](#); selected entitie: bear in mind that several mechanisms may be operative in the same patient.

### Infectious Enterocolitis

Intestinal diseases of microbial origin are marked principally by diarrhea and sometimes by ulcero large intestine. *Infectious enterocolitis is a global problem of staggering proportions, causing more and accounting for up to one-half of deaths in children younger than 5 years of age in some count industrialized nations, infectious enterocolitis is still responsible for approximately 1.5 episodes of year, second only to the common cold in frequency. About 500 infants and young children die of c States. Moreover, diarrhea is the most common health problem encountered by the more than 30 per year.*

Among the most common offenders are rotavirus, calciviruses, and enterotoxigenic *Escherichia c* diarrhea; the major offenders vary with the age, nutrition, and immune status of the host, environn measures), and special predispositions such as foreign travel, exposure to more virulent organism dislocation. In 40% to 50% of cases, the specific agent cannot be isolated.

**Table 15-7. Major Causes of Diarrheal Illnesses**

<b>Secretory Diarrhea</b>
Infectious: viral damage to surface epithelium
Rotavirus
Norwalk virus
Enteric adenoviruses
Infectious: enterotoxin-mediated
<i>Vibrio cholerae</i>
<i>Escherichia coli</i>

<i>Bacillus cereus</i>
<i>Clostridium perfringens</i>
Neoplastic: tumor elaboration of peptides or serotonin
Excessive laxative use
<b>Osmotic Diarrhea</b>
Lactulose <sup>®</sup> therapy (for hepatic encephalopathy, constipation)
Prescribed gut lavage for diagnostic procedures
Antacids (MgSO <sub>4</sub> and other magnesium salts)
<b>Exudative Diseases</b>
Infectious: destruction of the epithelial layer
<i>Shigella</i> spp.
<i>Salmonella</i> spp.
<i>Campylobacter</i> spp.
<i>Entamoeba histolytica</i>
Idiopathic inflammatory bowel disease
<b>Malabsorption</b>
Defective intraluminal digestion
Defective mucosal-cell absorption
Reduced small intestinal surface area
Lymphatic obstruction
Infectious: impaired mucosal-cell absorption
<i>Giardia lamblia</i>
<b>Deranged Motility</b>
Decreased intestinal retention time
Surgical reduction of gut length
Neural dysfunction, including irritable bowel syndrome
Hyperthyroidism
Decreased motility (increased intestinal retention time)
Surgical creation of a "blind" intestinal loop
Bacterial overgrowth in the small intestine

Worldwide, intestinal parasitic disease and protozoal infections are also major causes of chronic diarrhea. Collectively, they affect more than one-half of the world's population, because they are endemic in many areas. In addition to the lower alimentary tract infections, only selected examples are described here.

### *Viral Gastroenteritis*

Viral infection of superficial epithelium in the small intestine destroys these cells and their absorptive capacity. The destruction of intestinal villi with immature enterocytes and relative preservation of crypt secretory cells leads to malabsorption, which is compounded by an osmotic diarrhea from incompletely absorbed nutrients.

Symptomatic disease is caused by several distinct groups of viruses:

*Rotavirus* accounts for an estimated 130 million cases and 0.9 million deaths worldwide per year. It is the leading cause of childhood enterocolitis in the United States. The affected population is children 6 months to 2 years of age. The prodrome for the development of diarrhea after infection is 2 days, and the illness lasts 3 to 7 days. *Caliciviruses*, particularly the *Norwalk virus*, are responsible for most cases of nonbacterial gastroenteritis in older children and adults. Infection in young children is unusual. Additional viruses associated with acute gastroenteritis, almost always by person-to-person contact, include several subtypes of *adenovirus* (Ad40 and Ad41).

### *Bacterial Enterocolitis*

Several mechanisms underlying bacterial diarrheal illness were discussed briefly in [Chapter 9](#) but are not discussed in detail here.



Several mechanisms underlying bacterial diarrheal illness were discussed briefly in [Chapter 9](#) but

*Ingestion of preformed toxin*, present in contaminated food. Major offenders of food poison spp., and *Clostridium perfringens*. One may also ingest preformed neurotoxins, exemplified by *Botulinum toxin*, which proliferate within the gut lumen and elaborate an enterotoxin. *In* which proliferate, invade, and destroy mucosal epithelial cells.

Infection by toxigenic or enteroinvasive organisms involves bacterial replication in the gut and dep

1. *The ability to adhere to mucosal epithelial cells*. To produce disease, ingested organisms must not be swept away by the fluid stream. Adherence is often mediated by plasmid-coded adhesins (e.g., *E. coli* fimbriae on the surface of the organism).
2. *The ability to elaborate enterotoxins*. Enterotoxigenic organisms produce polypeptides that act as secretagogues, which activate secretion without inducing cell damage; cholera toxin, the classic prototype toxin of this type. Alternatively, they may be cytotoxins, which cause direct epithelial damage. The enterotoxigenic strains of *E. coli* are the main cause of traveler's diarrhea.
3. *The capacity to invade*. Enteroinvasive organisms such as *Shigella* possess a large virulence plasmid that mediates epithelial cell invasion. This is followed by intracellular proliferation, cell lysis, and cell-to-cell spread. *Shigella* is the cause of endemic bacillary dysentery in locations of poor hygiene in developing and developed countries. *Salmonella typhi*, causing typhoid fever, and *Yersinia enterocolitica* pass through mucosa and the bloodstream. Other species of *Salmonella*, such as *S. enteritidis* and *S. typhimurium*, are major causes of food poisoning in the United States, through the ingestion of contaminated eggs, chicken, and ground beef.

The major bacteria giving rise to *bacterial enterocolitis* are presented in [Table 15-8](#).

**Table 15-8. Major Causes of Bacterial Enterocolitis**

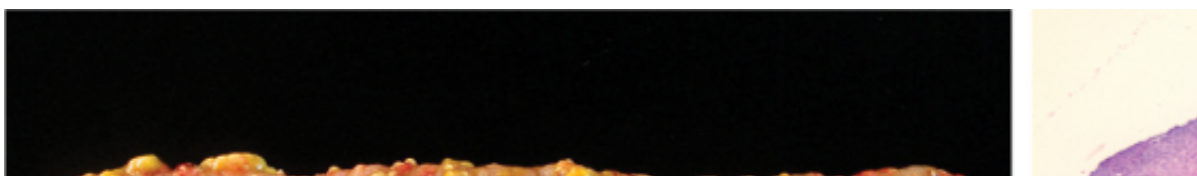
Organism	Pathogenic Mechanism	Source	Clinical Features
<i>Escherichia coli</i>			
ETEC	Cholera-like toxin, no invasion	Food, water	Traveler's diarrhea
STEC	Shiga toxin, no invasion	Undercooked beef products	Hemorrhagic colitis (14)
EPEC	Attachment, enterocyte effacement, no invasion	Weaning foods, water	Watery diarrhea, infantile
EIEC	Invasion, local spread	Cheese, water, person to person	Fever, pain, diarrhea
<i>Salmonella</i> spp.	Invasion, translocation, lymphoid inflammation, dissemination	Milk, beef, eggs, poultry	Fever, pain, diarrhea, intestinal infection
<i>Shigella</i> spp.	Invasion, local spread	Person to person, low inoculum	Fever, pain, diarrhea
<i>Campylobacter</i>	?Toxins, invasion	Milk, poultry, animal contact	Fever, pain, diarrhea, animal reservoirs
<i>Yersinia enterocolitica</i>	Invasion, translocation, lymphoid inflammation, dissemination	Milk, pork	Fever, pain, diarrhea, intestinal infection
<i>Vibrio cholerae</i> , other <i>Vibrio</i> spp.	Enterotoxin, no invasion	Water, shellfish, person to person	Watery diarrhea, cholera
<i>Clostridium difficile</i>	Cytotoxin, local invasion	Nosocomial environmental spread	Fever, pain, bloody stool, nosocomial acquisition
<i>Clostridium perfringens</i>	Enterotoxin, no invasion	Meat, poultry, fish	Watery diarrhea, food poisoning
<i>Mycobacterium tuberculosis</i>	Invasion, mural inflammatory foci with necrosis and scarring	Contaminated milk, swallowing of coughed-up organisms	Chronic abdominal pain, stricture, perforation

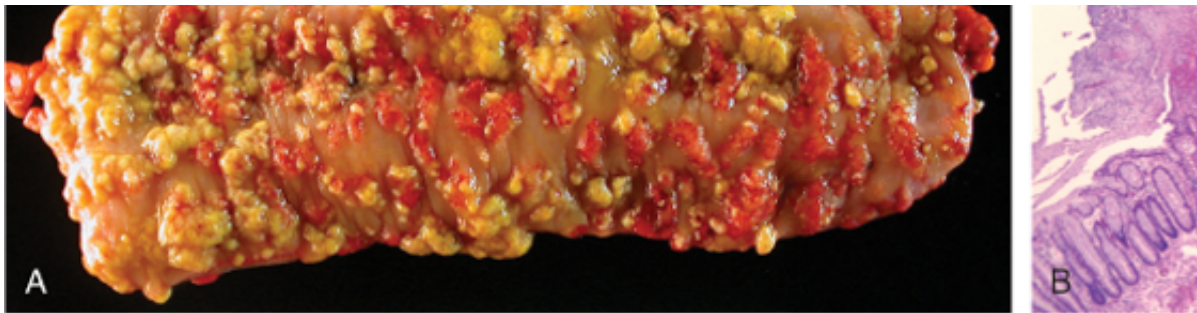
ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin-producing *E. coli* (also called EHEC, enterohemorrhagic *E. coli*); EPEC, enteropathogenic *E. coli*; EIEC, enteroinvasive *E. coli*.

## Morphology

Given the multitude of bacterial pathogens, the pathologic manifestations of small intestinal bacterial disease are quite variable. **Most bacterial infections exhibit a nonspecific inflammatory response in the surface epithelium, with an increased mitotic rate in mucosal crypts and surface epithelial cells. There follows hyperemia and edema of the lamina propria and neutrophilic infiltration into the lamina propria and epithelial layer.** In more severe cases, such as with cytotoxin-producing or enteroinvasive bacteria, progressive destruction of the mucosa, ulceration, and severe submucosal inflammation. Notable features of particular infections include:

1. ***E. coli*** (a particularly versatile organism):  
Enterotoxigenic strains (ETEC) affect the small intestine, with histologic changes similar to those of cholerae (described below). The Shiga toxin-producing strain (STEC) causes a severe disease in the right colon, with hemorrhage and ulceration. It may be followed by the hemolytic uremic syndrome ([Chapter 14](#)). The most common strain of *E. coli* in North America. Enteropathogenic strains (EPEC) are associated with producing villus blunting. Enteroinvasive strains (EIEC) affect the colon in a manner similar to *Shigella*. Enteraggregative strains (EAEC) also affect the colon, with a "brick" pattern of adherence in tissues.
2. ***Salmonella*** species are a major cause of common-source outbreaks of enteric disease. They cause a localized mucosal disease primarily in the ileum and colon (as with *S. enteritidis* and others). *S. typhimurium* generally causes a self-limited gastroenteritis with vomiting and fever. Life-threatening systemic illness is the hallmark of *S. typhi*, where intestinal invasion leads to systemic dissemination (**typhoid fever**). Typhoid fever is characterized by **bacteremia** (first week), widespread involvement of macrophages with **foci of necrosis in the liver** (second week), and **ulceration of Peyer's patches with bleeding and ulceration** (third week). **Gallbladder colonization** produces chronic infection also may affect the joints, bones, meninges, and other sites.
3. ***Shigella*** affects primarily the distal colon, producing acute mucosal inflammation and ulceration.
4. ***Campylobacter jejuni*** (and other species) affects the small intestine, appearing as many superficial ulcers, mucosal inflammation, and exudates.
5. ***Yersinia enterocolitica* and *Y. pseudotuberculosis*** affect the ileum, appearing as patchy invasion leads to mesenteric lymph node enlargement with necrotizing enteritis. Spread may lead to peritonitis, pharyngitis, and pericarditis.
6. ***V. cholerae*** (cholera) affects the small intestine, especially more proximally. The mucosa is essentially intact, with only mucus-depleted crypts.
7. ***Clostridium difficile*** is a normal gut organism, but cytotoxin-producing strains are associated with systemic antibiotic use. A distinctive **pseudomembranous colitis** is produced, named from the plaquelike adhesion of fibrinopurulent debris and mucus to the mucosa ([Fig. 15-27](#)). These are not true "membranes," because the coagulum is not attached to the mucosal layer.
8. ***C. perfringens*** shows features similar to *V. cholerae* but with some epithelial damage and produce a severe necrotizing enterocolitis with perforation.
9. Ingested ***Mycobacterium tuberculosis*** incites chronic inflammation and granuloma formation in the mucosal lymphoid tissue-particularly Peyer's patches in the terminal ileum-[and cecum](#) ([Chapter 13](#)).

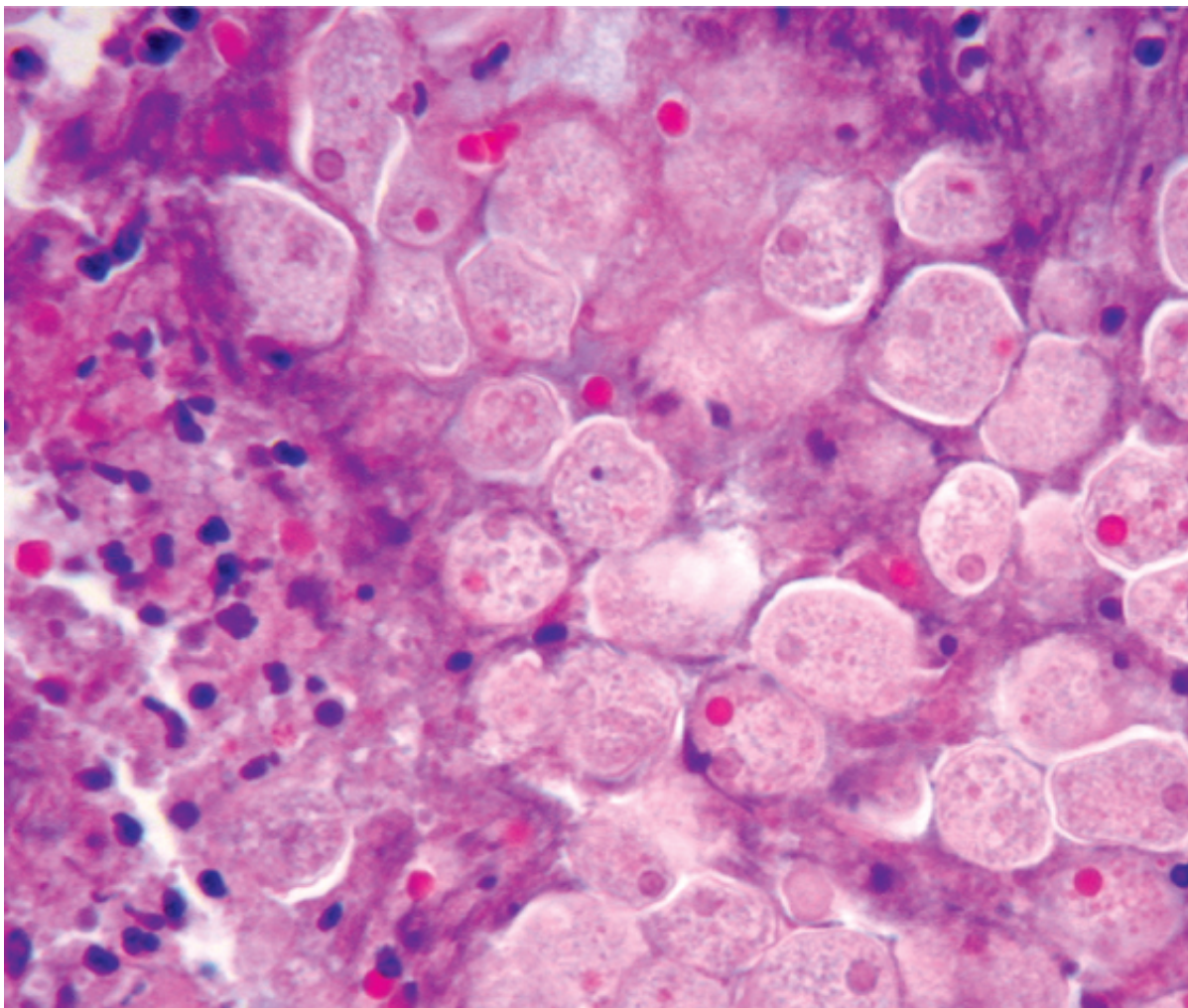




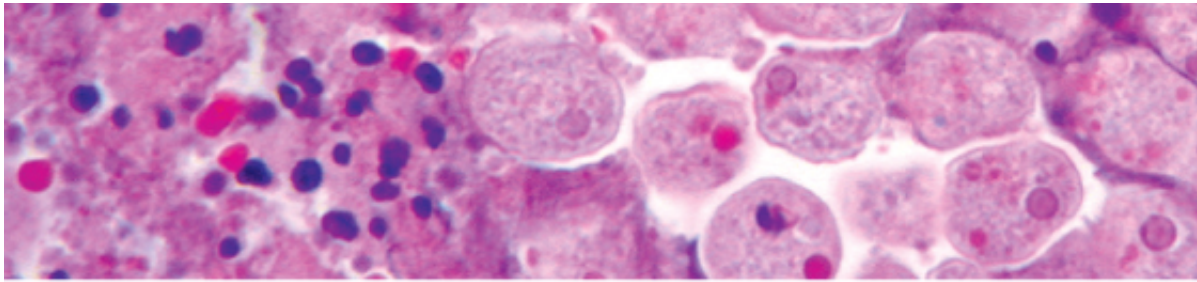
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 Figure 15-27 Pseudomembranous colitis from *Clostridium difficile* infection. **A**, Gross photograph showing plaques to a reddened colonic mucosa. **B**, Low-power micrograph showing superficial mucosal erosion, an adherent pseu

### Protozoal Infection

*Entamoeba histolytica* is a dysentery-causing protozoal parasite spread by fecal-oral contamination. The parasites enter the colon through the mucosa and burrow down into the submucosa (Fig. 15-28); the organisms then fan out laterally to form a shallow ulcer with a narrow neck and broad base. There may be very little inflammatory infiltrate within the ulcer. In about 40% of cases, parasites penetrate portal vessels and embolize to the liver to produce solitary, or less often multiple, abscesses. Some abscesses may exceed 10 cm in diameter. Some patients may present with amebic liver abscesses, without a primary focus in the colon. In the absence of the intestinal lesions, there is a scant inflammatory reaction at the margin. Occasional amebic abscesses may involve the heart, kidneys, and even brain. Such abscesses remain long after the acute intestinal illness has passed.







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Figure 15-28 *Entamoeba histolytica* in the colon. Some organisms are ingesting

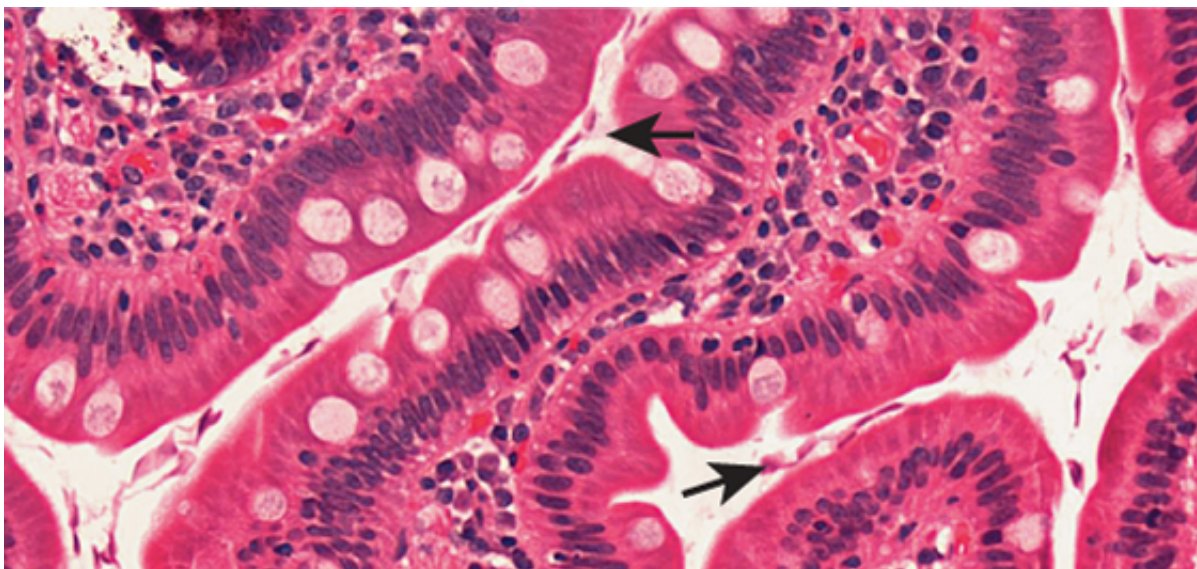
*Giardia lamblia* is an intestinal protozoan spread by water contaminated with feces. *Giardia* organisms do not appear to invade (Fig. 15-29). Small intestine morphology may range from virtually normal to mixed inflammatory infiltrate in the lamina propria. A malabsorptive diarrhea seems to result from a mechanism that is not understood.

*Cryptosporidiosis* has emerged as an important cause of diarrhea in animals and humans worldwide. It accounts for as much as 20% of all cases of childhood diarrhea in developing countries and is a common complication of AIDS. Water-borne contamination and an increased population at risk for zoonotic infections have led to an increase in this disease.

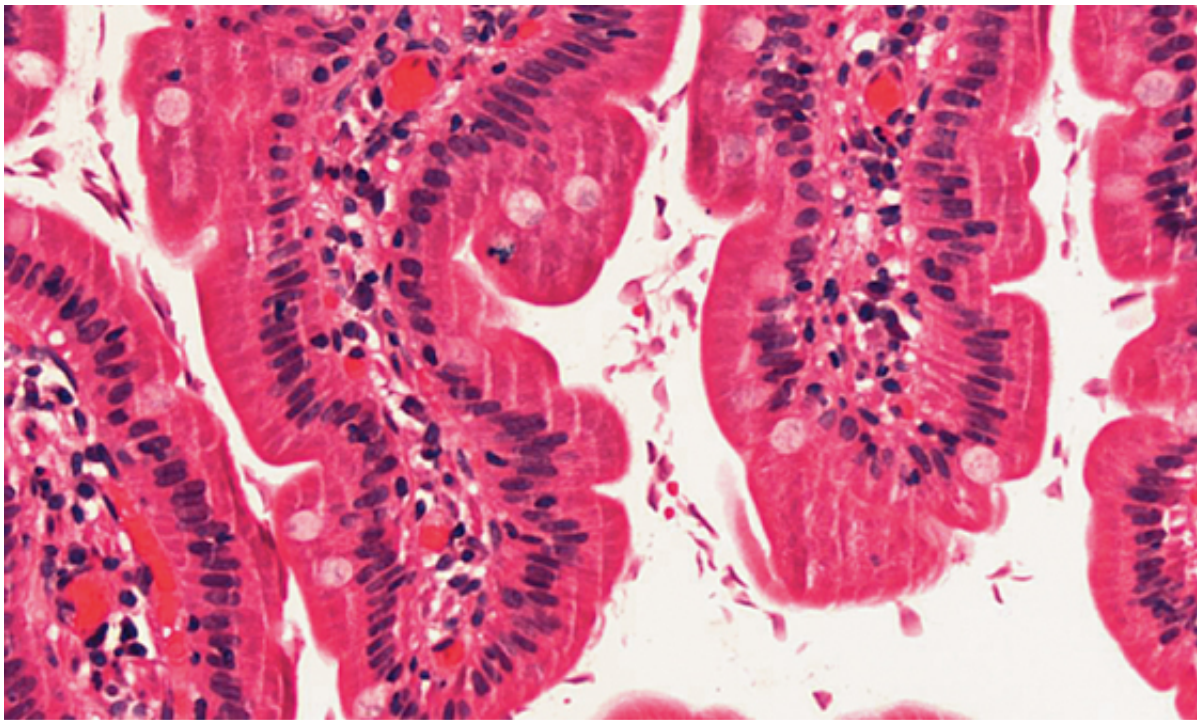
#### Clinical Features

The clinical features of viral and protozoal infection have been briefly noted already. At the risk of oversimplification, the clinical picture takes the following forms:

**Ingestion of preformed bacterial toxins.** Symptoms develop within a matter of hours; explosive onset heralds an illness that passes within a day or so. Ingested systemic neurotoxins, as in botulism, can be fatal, and respiratory failure may ensue. **Infection with enteric pathogens.** With ingestion of enteric pathogens, symptoms may take hours to days to develop. If the primary pathogenic mechanism is a cytotoxin or an enteroinvasive process, the primary mechanism is a cytotoxin or an enteroinvasive process. Traveler's diarrhea (e.g., *Campylobacter*) occurs after ingestion of feces-contaminated food or water; it begins abruptly and subsides within a few days. *Yersinia* and *Mycobacterium* infections may also present as subacute diarrheal illnesses. In some cases, enteroinvasive organisms can mimic, or even precipitate, acute onset of idiopathic inflammatory bowel disease.







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Figure 15-29 *Giardia lamblia*. Trophozoites (arrows) of the organism immediately adjacent to the duodenal surface  
of Drs. Melissa Upton and Paul Swanson, Department of Pathology, University of Washington

In general, bacterial enterocolitis is a more severe illness than viral disease. The complications of fluid loss or destruction of the intestinal mucosal barrier and include dehydration, sepsis, and peritonitis ensues rapidly without quick intervention, particularly in the very young.

A distressing gastrointestinal emergency in neonates, particularly those who are premature or of low birth weight, is necrotizing enterocolitis. This acute, necrotizing inflammation of the small and large intestines is thought to result from a combination of immaturity of the neonatal gut, colonization and invasion by pathogenic organisms, and secondary factors. The terminal ileum and ascending colon may be affected, or the entire small and large intestines may be involved. In severe cases the entire bowel wall becomes hemorrhagic and gangrenous, necessitating surgical resection. Signs and symptoms include abdominal distention, tenderness, ileus, and diarrhea with occult or frank blood. Onset of gangrene is threatening.

## SUMMARY

**Enterocolitis (Diarrheal Diseases)** The major types of diarrheal diseases are secretory, exudative, malabsorption-related, and due to deranged motility. Secretory diarrhea is caused by viruses or enterotoxin-producing bacteria such as *E. coli*; in general, bacterial enterocolitis is a more serious disease than viral disease. *Salmonella* spp. and *Shigella* spp. cause bacterial enterocolitis. *Salmonella* infection is a very common cause of food poisoning. *S. typhi* causes typhoid fever. Bacterial enterocolitis may result from the ingestion of preformed enterotoxins, or take the form of an insidious infection that leads to inflammatory bowel disease. The most common agents of enterocolitis are *Entamoeba histolytica*, *Giardia lamblia* and *Cryptosporidium parvum*.

## Malabsorption Syndromes

Malabsorption is characterized by defective absorption of fats, fat-soluble and other vitamins, proteins, minerals, and water. The most common presentation is chronic diarrhea; the hallmark of malabsorption is weight loss.

(excessive fat content of the feces). At the most basic level, *malabsorption is the result of disturbed digestive functions*:

*Intraluminal digestion*, in which proteins, carbohydrates, and fats are enzymatically broken down with saliva, receives a major boost from gastric peptic digestion, and continues in the small intestine with the secretin-stimulated secretion and the emulsive action of bile. *Mucosal absorption* in which water, electrolytes, and nutrients are transported into the cell. Absorbed fatty acids are converted to triglycerides and are assembled into chylomicrons. Disturbances can be caused by primary mucosal cell abnormalities or reabsorption defects. Other cases result from mucosal infections. *Nutrient delivery*, involving the delivery of nutrients to the lymphatics. Disturbances may be caused by congenital defects, or be secondary to tuberculosis.

A host of disorders interrupt these three digestive functions, either directly or indirectly (Table 15-9). The most commonly encountered in the United States are *pancreatic insufficiency*, *celiac disease*, and *Crohn's disease*. The last two of the most common malabsorption syndromes caused by defects in either intraluminal digestion or mucosal absorption are discussed under the heading "Inflammatory Bowel Disease."

#### Defects of Intraluminal Digestion

**Table 15-9. The Major Malabsorption Syndromes**

<b>Defective Intraluminal Digestion</b>
Digestion of fats and proteins
Pancreatic insufficiency, due to pancreatitis or cystic fibrosis
Zollinger-Ellison syndrome, with inactivation of pancreatic enzymes by excess gastric acid secretion
Solubilization of fat, due to defective bile secretion
Ileal dysfunction or resection, with decreased bile salt uptake
Cessation of bile flow from obstruction, hepatic dysfunction
Nutrient preabsorption or modification by bacterial overgrowth
Distal ileal resection or bypass
Total or subtotal gastrectomy
<b>Primary Mucosal Cell Abnormalities</b>
Defective terminal digestion
Disaccharidase deficiency (lactose intolerance)
Bacterial overgrowth, with brush-border damage
Defective transepithelial transport
Abetalipoproteinemia
<b>Reduced Small Intestinal Surface Area</b>
Gluten-sensitive enteropathy (celiac disease)
Short-gut syndrome, after surgical resections
Crohn disease
<b>Infections</b>
Acute infectious enteritis
Parasitic infestation
Tropical sprue
Whipple disease
<b>Lymphatic Obstruction</b>
Lymphoma
Tuberculosis and tuberculous lymphadenitis

Typical features of defective intraluminal digestion are an *osmotic diarrhea* from undigested nutrients (e.g., undigested fat in the stool). The latter can arise either from inadequate action of pancreatic lipase or from obstruction of bile secretion by hepatic bile secreted into the gut lumen. The most common causes are *pancreatic insufficiency* and *celiac disease*.

Crohn disease, discussed below. Other causes are intestinal bacterial overgrowth, cholestatic liver disease, as extensive ileal resection and gastrojejunostomy.

### *Defects of Mucosal Absorption*

*Lactose intolerance and abetalipoproteinemia* are examples of diseases caused by a specific defect of the intestinal mucosa. *Lactose intolerance* is caused by the deficiency of disaccharidase (*lactase*). The inheritance is autosomal recessive. The consequence, because in infants it produces milk intolerance, leading to diarrhea, weight loss, and failure to thrive, is common among adults, particularly North American blacks. Aside from the need to avoid milk products, the intestinal mucosa is morphologically normal. Diagnosis is most readily made by a lactose tolerance test, which reflects bacterial overgrowth in the presence of excess intraluminal carbohydrate.

Deficiency of apolipoprotein B (*abetalipoproteinemia*) makes the mucosal epithelial cell unable to assemble dietary lipids into chylomicrons, which are then secreted into intestinal lymphatics. The mucosa contains vacuolated lipid inclusions, but the mucosa is otherwise normal. This deficiency causes a significant failure to thrive. There are systemic lipid membrane abnormalities as well, readily observed as characteristic burr cell transformation termed *acanthocytosis*.

*Celiac disease, also known as gluten-sensitive enteropathy*, is the prototype of a noninfectious cause of malabsorption. It is characterized by a reduction in small intestinal absorptive surface area. Celiac disease is believed to be quite common in Europe and in the United States, and many patients have subclinical disease. The basic disorder is an autoimmune sensitivity to gluten, the component of wheat and related grains (oat, barley, and rye) that contains gliadin. Gliadin peptides are efficiently presented by antigen-presenting cells in the lamina propria of the small intestine, driving an immune response to gluten. There is hence a strong genetic susceptibility, with 95% of patients having HLA-DQ8, and most of the remainder having HLA-DQ2. Early exposure of the immature immune system of the child is a prominent cofactor for manifestation of clinically overt celiac disease later in life.

The small intestinal mucosa, when exposed to gluten, accumulates intraepithelial CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells sensitized to gliadin. The CD8<sup>+</sup> T cells that accumulate in the gut may not be specific for gliadin but may recognize stress-induced molecules on epithelial cells via the NK cell-associated NKG2D receptor, which recognizes stress-induced molecules on epithelial cells. The result from epithelial cell stress, perhaps induced by gliadin sensitivity, and CD8<sup>+</sup> T cell-mediated cytotoxicity are probably also involved (based on the HLA associations), but their role and the role of antigen-presenting cells in the precise mechanism, the effect of the immune response may be total flattening of mucosal villi, affecting the proximal more than the distal small intestine. In addition, lymphocytes and other inflammatory cells infiltrate the lamina propria.

The age of presentation with symptomatic diarrhea and malnutrition varies from infancy to mid-adulthood, but is usually met with dramatic improvement. There is, however, a low long-term risk of malignant disease, with an increased rate of intestinal lymphomas, especially T-cell lymphomas, are disproportionately represented; other associated malignancies include gastric and breast carcinomas. In some patients with celiac disease there is an associated skin disorder (dermatitis herpetiformis) (22).

*Tropical sprue and Whipple disease* are two disorders that exemplify malabsorption syndromes. Tropical sprue resembles celiac disease in symptomatology but occurs almost exclusively in persons living in the tropics. The causal agent has been clearly identified, but the appearance of malabsorption within days or a few weeks after infection strongly implicates an infectious process, as does prompt response to broad-spectrum antibiotics. The disease varies from near normal to a severe diffuse enteritis with villus flattening. In contrast to celiac disease, the mucosa of the small intestine.

Whipple disease is a rare systemic infection that may involve any organ of the body but principally the small intestine, heart, and joints. The hallmark of Whipple disease is a small intestinal mucosa laden with foamy macrophages in the lamina propria. The causal organism is a gram-positive and culture-resistant bacterium, *Tropheryma whippelii*. Although *T. whippelii* is not an obligate intracellular pathogen, phagocytosed organisms and debris persist within lamina propria macrophages for years, without causing inflammation. Occurring principally in males, Whipple disease causes a malabsorptive syndrome occasionally accompanied by lymphadenopathy, arthritis, and obscure central nervous system complaints. Response to antibiotic therapy is usually prompt, but

obscure central nervous system complaints. Response to antibiotic therapy is usually prompt, but

### *Clinical Features*

Clinically, the malabsorption syndromes resemble each other. The passage of abnormally bulky, fatty stools is a prominent feature of malabsorption, accompanied by weight loss, anorexia, abdominal distention, and wasting. The consequences of malabsorption affect many organ systems:

*Hematopoietic system:* anemia from iron, pyridoxine, folate, or vitamin B<sub>12</sub> deficiency (vitamin K deficiency causes bleeding from vitamin K deficiency (a fat-soluble vitamin))  
*Musculoskeletal system:* osteoporosis from calcium and vitamin D deficiency  
*Endocrine system:* amenorrhea, impotence, and hyperparathyroidism from protracted calcium and vitamin D deficiency  
*Skin:* dermatitis and hyperkeratosis from deficiencies of essential fatty acids, and niacin; mucositis from vitamin deficiencies  
*Nervous system:* peripheral neuropathy from vitamin deficiencies



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## INFLAMMATORY BOWEL DISEASE

Crohn disease and ulcerative colitis are chronic relapsing inflammatory disorders of unknown origin (inflammatory bowel disease (IBD)), which share many common features. *They result from an abnormal flora of the gut, and probably against some self antigens, in genetically susceptible individuals. The Crohn disease involves a portion of the gastrointestinal tract from esophagus to anus but most often involves the ileum; it is characterized by a granulomatous inflammation. Ulcerative colitis is a nongranulomatous disease limited to the colon.* Separately, the pathogenesis of these two forms of IBD will be considered.

### *Etiology and Pathogenesis*

The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between the host immune system, such as luminal microbes, dietary antigens, and endogenous inflammatory mediators that regulate inflammation and maintain the integrity of the mucosa. The search for the causes of loss of this balance in ulcerative colitis has revealed many parallels, but the origins of *both diseases remain unexplained*. The pathogenesis of IBD involves genetic susceptibility, failure of immune regulation, and triggering by environmental factors. On each of these contributors. It is important to note that Crohn disease and ulcerative colitis differ in their clinical history of the disease, pathological aspects, and in the types of therapies and responses to treatment.

### Genetic Predisposition

There is little doubt that genetic factors are important in the occurrence of IBD. First-degree relatives of patients with IBD develop the disease, and 15% of persons with IBD have affected first-degree relatives. In keeping with this, dysfunction, both Crohn disease and ulcerative colitis have been linked to specific major histocompatibility complex (MHC) genes. Ulcerative colitis has been associated with *HLA-DRB1*, whereas *HLA-DR7* and *DQ4* alleles are associated with Crohn disease cases in North American white males. Much recent interest has focused on association with CARD15 genes. A gene called *NOD2* (or *CARD15*) is mutated in as many as 25% of Crohn disease patients. The NOD2 protein is an intracellular receptor for muramyl dipeptide, a component of the cell walls of many bacteria that elicit host responses to these bacteria. The protein is expressed in Paneth cells. The disease-associated mutation impairs the response to the bacteria, thus allowing chronic infections to be established in the intestine and promoting inflammation via NOD2-independent pathways. Alternatively, the disease-associated form of NOD2 may promote excessive responses to bacteria. Another gene that has recently been found to be associated with Crohn disease and ulcerative colitis is the *IL-23 receptor* (*IL-23R*) gene. IL-23 is a cytokine that promotes the production of IL-17 by T cells, and IL-17 is a key cytokine in reactions in IBD and other chronic inflammatory diseases. It is not known if or how the mutant IL-23 receptor affects these reactions.

### Immunologic Factors

It is not known whether the immune responses in IBD are directed against self-antigens of the intestine or against microbial antigens. The following general comments can be made about the immunologic responses in IBD.

In both Crohn disease and ulcerative colitis the primary damaging agents appear to be CD4+ T cells. In ulcerative colitis, antibodies and antitropomyosin antibodies detected in persons with ulcerative colitis do not appear to be pathogenic. It has long been thought that Crohn disease is the result of a chronic delayed-type hypersensitivity reaction mediated by Th1 cells. However, recent results from mouse models of IBD suggest that the disease is mediated by the secretion of the cytokine IL-17 by a recently discovered subset of CD4+ T cells that is being called Th17. In animal models ulcerative colitis may be caused by activation of Th2 cells, IL-4, the signature cytokine of Th2 cells, has not been found, suggesting that in ulcerative colitis there may not be a predominant class of T cell. In Crohn disease, the cytokine TNF (see [Chapter 2](#)) may play an important pathogenic role in Crohn disease. This is supported by the fact that treatment with TNF antagonists in this disorder.

### Microbial Factors

#### Microbial Factors

The sites affected by IBD-the distal ileum and the colon-are awash in bacteria. While there is no evidence by microbes, it is quite likely that microbes provide the antigenic trigger to a fundamentally dysregulated immune system strengthened by the observations that in murine models, IBD develops in the presence of normal flora.

To summarize, IBD is a heterogeneous group of diseases characterized by an exaggerated and dysregulated immune response. The tissue injury in IBD is likely to be initiated by diverse genetic and immunologic pathways that include environmental factors including microbes and their products.

Inflammation is the final common pathway for the pathogenesis of IBD. Both the clinical manifestations and the histologic findings of IBD are ultimately the result of activation of inflammatory cells-neutrophils initially and mononuclear cells later. The activation of these inflammatory cells cause nonspecific tissue injury. Inflammation causes (1) impaired intestinal motility, (2) loss of surface epithelial cell absorptive function. The inflammation ultimately causes outright rupture of the mucosal barrier and absorptive function. Collectively, these events give rise to the clinical and histologic characteristics of these diseases. Most current therapeutic interventions act entirely or partly through modulation of the immune system. Among diagnostic tests, the most useful is the detection of perinuclear antineutrophil cytoplasmic antibodies (pANCA) present in about 75% of persons with ulcerative colitis and only 11% of individuals with Crohn disease.

#### Crohn Disease

This disease may affect any level of the alimentary tract, from mouth to anus, but most commonly involves the terminal ileum. Originally described, the disease was thought to be limited to the ileum, and it was referred to as "terminal ileitis." However, it is now recognized that *Crohn disease must be viewed as a systemic inflammatory disease with predominant gastrointestinal involvement*. It is often accompanied by extra-intestinal complications of immune origin, such as uveitis, sacroiliitis, nodosum, bile duct inflammatory disorders, and obstructive uropathy with attendant nephrolithiasis.

When fully developed, Crohn disease is characterized by:

- Sharply limited transmural involvement of the bowel by an inflammatory process with mucosal ulceration
- Granulomas
- Fistula formation

#### Epidemiology

Worldwide in distribution, Crohn disease is much more prevalent in the United States, Great Britain, and Western Europe, and is rare in Asia and Africa. The incidence and prevalence of Crohn disease has been increasing in Asia and Africa. The annual incidence in the United States is 3 to 5 per 100,000 population, which is similar to the incidence of ulcerative colitis. It occurs at any age, from young childhood to advanced age, but the incidence peaks in the second and third decades of life, with a minor peak in the sixth and seventh decades. Females are affected more often than males. In the United States, Crohn disease appears to develop the disease two to five times more often than do nonwhites. In the United States, Crohn disease is five times more often among Jews than among non-Jews.

#### Morphology

In Crohn disease there is gross involvement of the small intestine alone in about 30%, of the small intestine and colon in 40%, and of the colon alone in about 30%. Crohn disease may involve the stomach, esophagus, and even mouth, but these sites are distinctly uncommon. **W Crohn disease is characterized by (1) sharply delimited and typically transmural inflammation of the bowel by an inflammatory process with mucosal damage, (2) the presence of granulomas in 40% to 60% of cases, and (3) fissuring with formation of fistulae.** The serosa becomes granular and dull gray and often the mesenteric fat wraps around the diseased segment ("creeping fat"). **The intestinal wall is rubbery and thick, the result of edema, and hypertrophy of the muscularis propria.** As a result, the lumen is almost always narrowed. In the small intestine this is seen radiographically as the "string sign," a thin stream of barium passing through the diseased segment. Strictures may occur in the colon but are usually less severe. **A characteristic feature of Crohn disease is the sharp demarcation of diseased bowel segments from adjacent normal bowel.** When several bowel segments are involved, the intervening bowel is essentially normal ("skip lesions").

In the intestinal mucosa, early disease shows focal mucosal ulcers resembling canyons (ulcers), edema, and loss of the normal mucosal texture. With progressive disease, serpentine linear ulcers, which tend to be oriented along the axis of the bowel (Fig. 10-10), intervene. Intervening mucosa tends to be relatively spared, it acquires a coarsely textured, cobblestone appearance. **Narrow fissures develop between the folds of the mucosa**, often penetrating deep into the wall all the way to the serosa. This may lead to adhesions with adjacent loops of bowel. Fissures lead to **fistula or sinus tract formation**, to adherent viscera, to the outside of the cavity to form a localized abscess.

By microscopic examination, the mucosa shows several characteristic features (Fig. 10-11): (1) **inflammation**, with neutrophilic infiltration into the epithelial layer and accumulation of **crypt abscesses**; (2) **ulceration**, which is the usual outcome of active disease; and (3) **damage** in the form of architectural distortion, atrophy, and metaplasia (including replacement of normal mucosa by intestinal metaplasia in the intestine). **Granulomas may be present anywhere in the alimentary tract in individuals with Crohn disease limited to one bowel segment. However, the absence of granulomas does not preclude a diagnosis of Crohn disease.** In diseased segments, the mucosa and muscularis propria are usually markedly thickened, and fibrosis affects all tissue layers. Lymphoid aggregates are scattered through the various tissue layers and in the extramural fat adjacent to the bowel.

Particularly important in persons with long-standing chronic disease are dysplastic mucosal epithelial cells. These may be focal or widespread, tend to increase with time, and are related to a fivefold to sixfold increased risk of carcinoma, particularly of the colon.

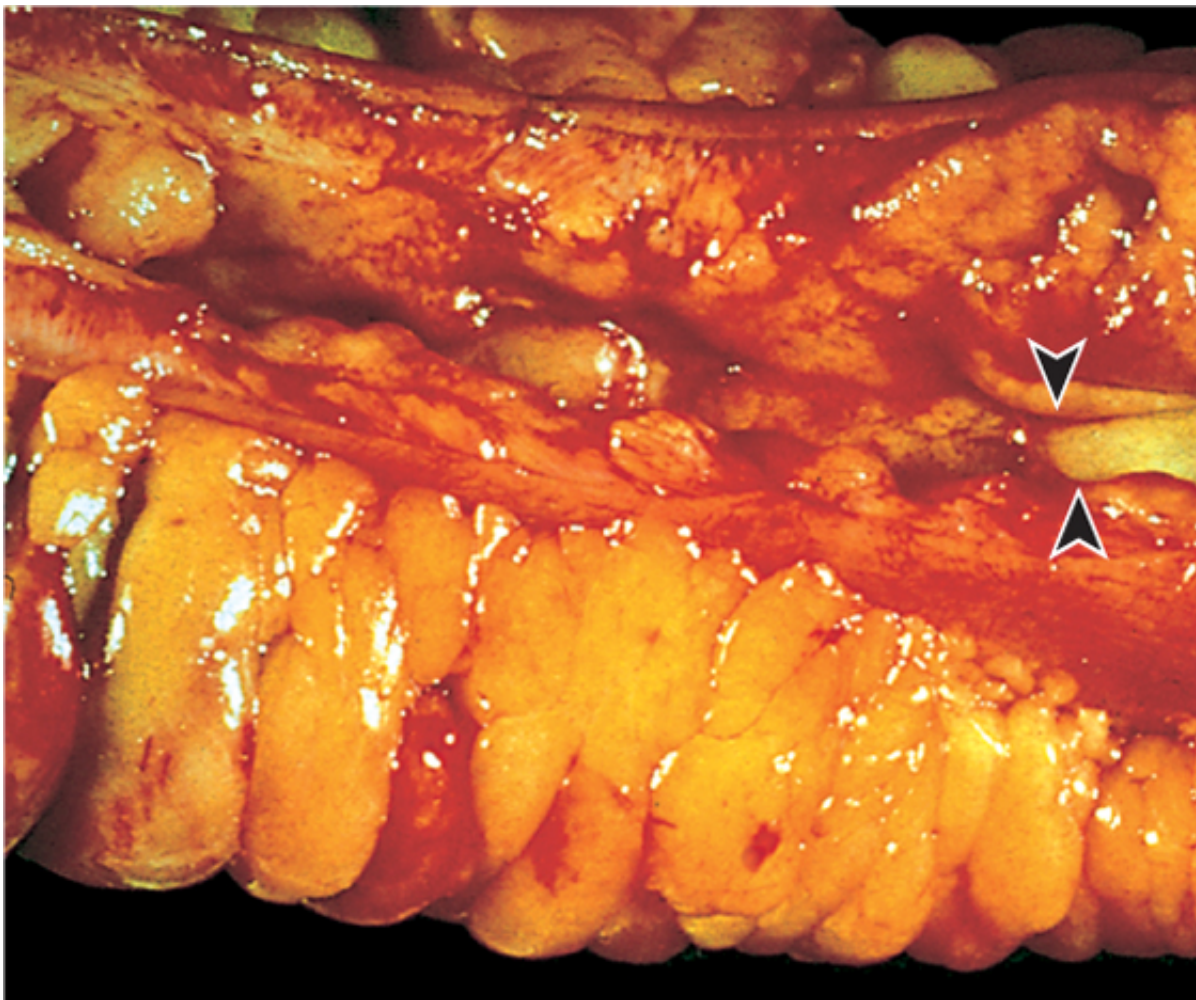
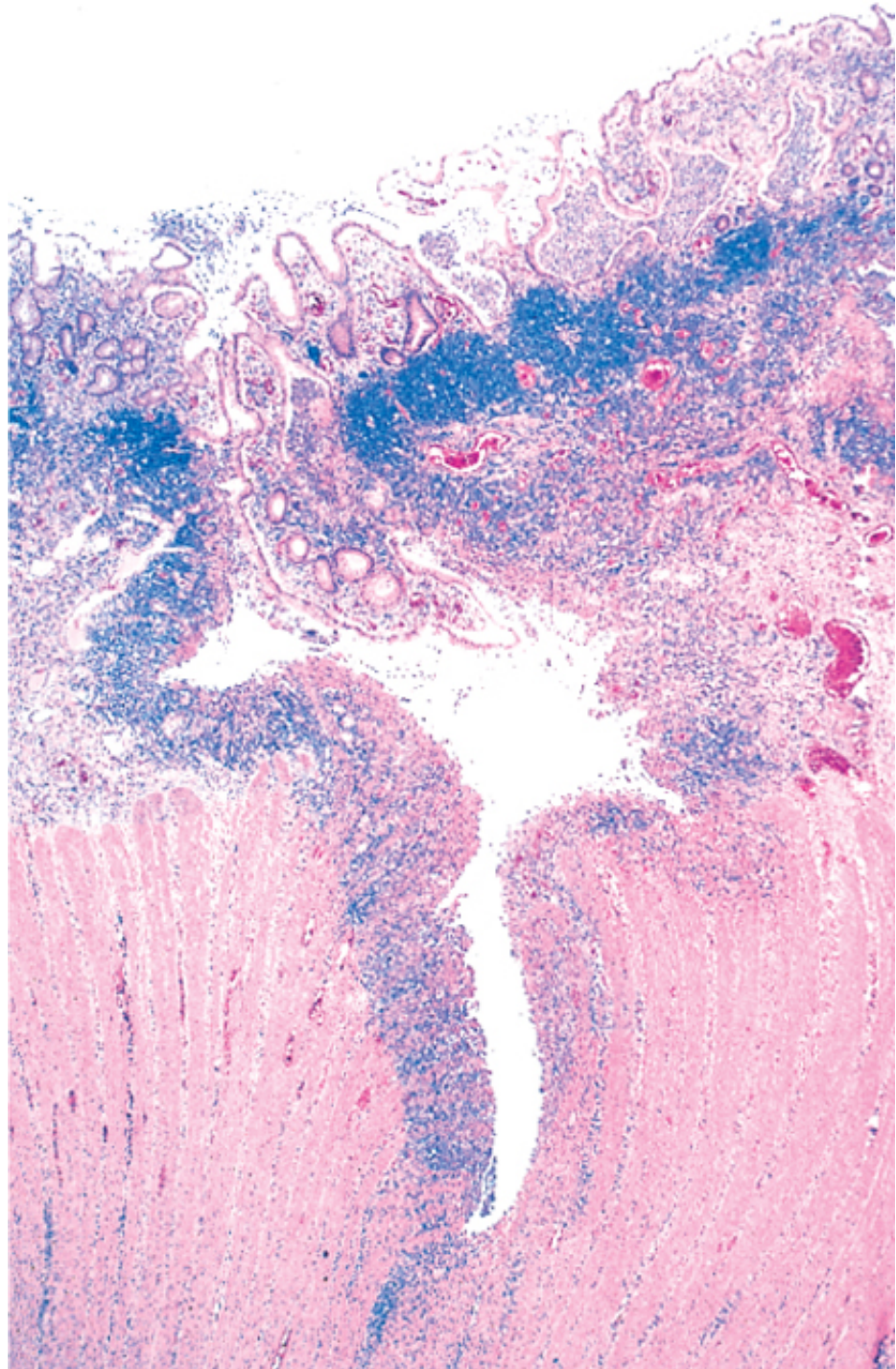




Figure 15-30 Crohn disease of the ileum showing narrowing of the lumen, bowel wall thickening, serosal extension, and ulceration of the mucosal surface (arrowheads).



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Figure 15-31 Crohn disease of the colon showing a deep fissure extending into the muscle wall, a second, shallow fissure extending into the intervening mucosa. Abundant lymphocyte aggregates are present, evident as dense blue patches of cells at

### *Clinical Features*



The presentation of Crohn disease is highly variable and unpredictable. The dominant manifestations are crampy abdominal pain, and fever lasting days to weeks. These manifestations usually begin in childhood. In young persons, the onset of the pain is so abrupt and the diarrhea so mild that abdominal examination is usually normal. Some melenas are present in about 50% of cases with colon involvement; it is usually rare in Crohn disease. In patients, after an initial attack, the manifestations remit either spontaneously or with therapy, but they often relapse, and intervals between successive attacks grow shorter. In 10% to 20% of persons with Crohn disease, after the initial attack may last for decades, and for a very fortunate few the first attack is the last. Most persons experience continuously active disease following their diagnosis. For the majority, the course fluctuates over years with clinically active disease. Superimposed on this course are the potential development of other intestinal manifestations mentioned earlier.

The debilitating consequences of Crohn disease include (1) *fistula* formation to other loops of bowel or to the perianal skin; (2) *abdominal abscesses* or peritonitis; and (3) *intestinal stricture* or obstruction, next to the most devastating events are massive intestinal bleeding, toxic dilation of the colon, or carcinoma of the colon. The increased risk for carcinoma is significant, it is substantially less than that associated with ulcerative colitis. Intrinsic to these two conditions, but may relate to the fact that in Crohn disease the affected bowel is discontinuous, thus reducing the risk of cancer.

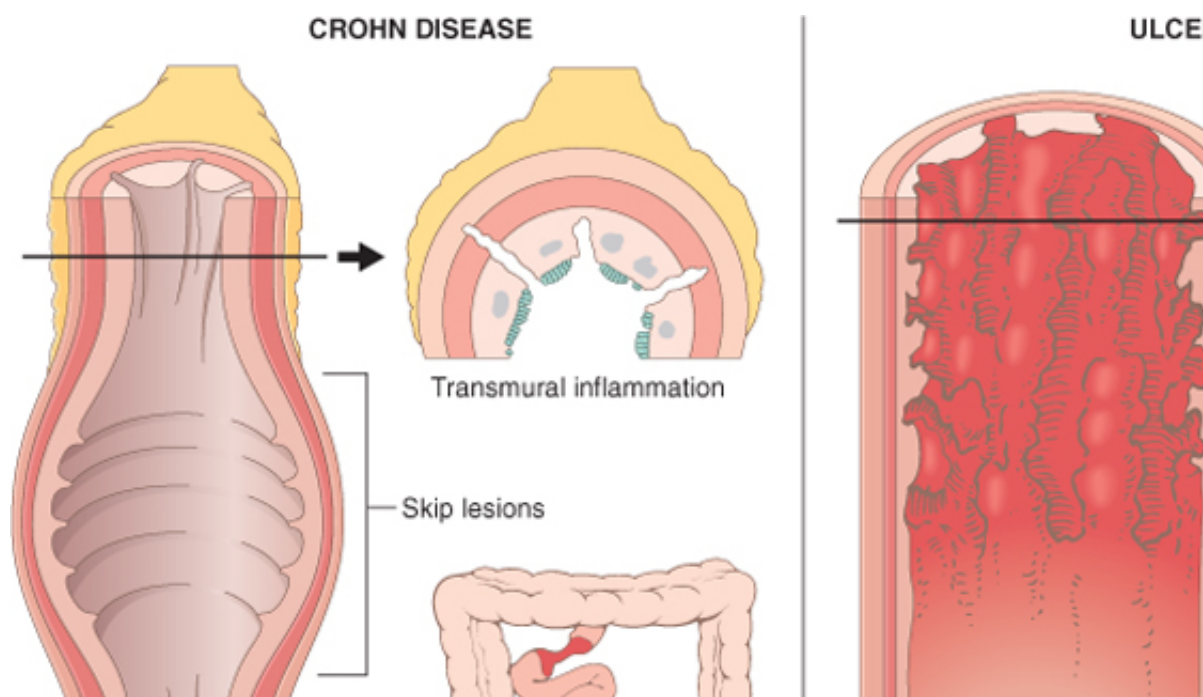
### Ulcerative Colitis

Ulcerative colitis is an ulceroinflammatory disease affecting the colon, which is limited to the mucosa and submucosa. In severe cases, ulcerative colitis begins in the rectum and extends proximally in a continuous fashion. Like Crohn disease, ulcerative colitis is a systemic disorder associated in some persons with migratory arthritis, spondylitis, uveitis, erythema nodosum, and hepatic involvement (pericholangitis and primary sclerosing cholangitis). The important differences between ulcerative colitis and Crohn disease (Fig. 15-32 and Table 15-10).

In ulcerative colitis:

Well-formed granulomas are absent. There are no skip lesions. The mucosal ulcers rarely extend through the mucosa. There is surprisingly little fibrosis. Mural thickening does not occur, and the serosal surface is usually normal. There is a high risk of carcinoma development.

### Epidemiology





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Figure 15-32 Comparison of the distribution patterns of Crohn disease and ulcerative colitis, and the different co

**Table 15-10. Distinctive Features of Crohn Disease and Ulcerative Colitis**

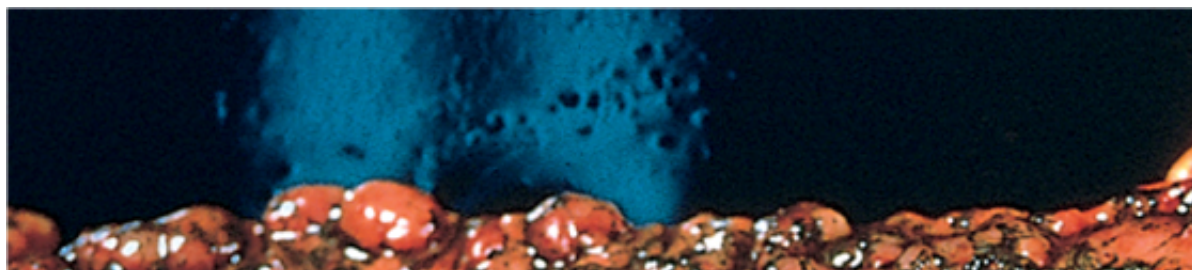
Feature	Crohn Disease (Small intestine)	Crohn Disease (C
<b>Macroscopic</b>		
Bowel region	Ileum ± colon†	Colon ± ileum
Distribution	Skip lesions	Skip lesions
Stricture	Early	Variable
Wall appearance	Thickened	Variable
Dilation	No	Yes
<b>Microscopic</b>		
Pseudopolyps	None to slight	Marked
Ulcers	Deep, linear	Deep, linear
Lymphoid reaction	Marked	Marked
Fibrosis	Marked	Moderate
Serositis	Marked	Variable
Granulomas	Yes (40% to 60%)	Yes (40% to 60%)
Fistulas/sinuses	Yes	Yes
<b>Clinical</b>		
Fat/vitamin malabsorption	Yes	Yes, if ileum
Malignant potential	Yes	Yes
Response to surgery‡	Poor	Fair

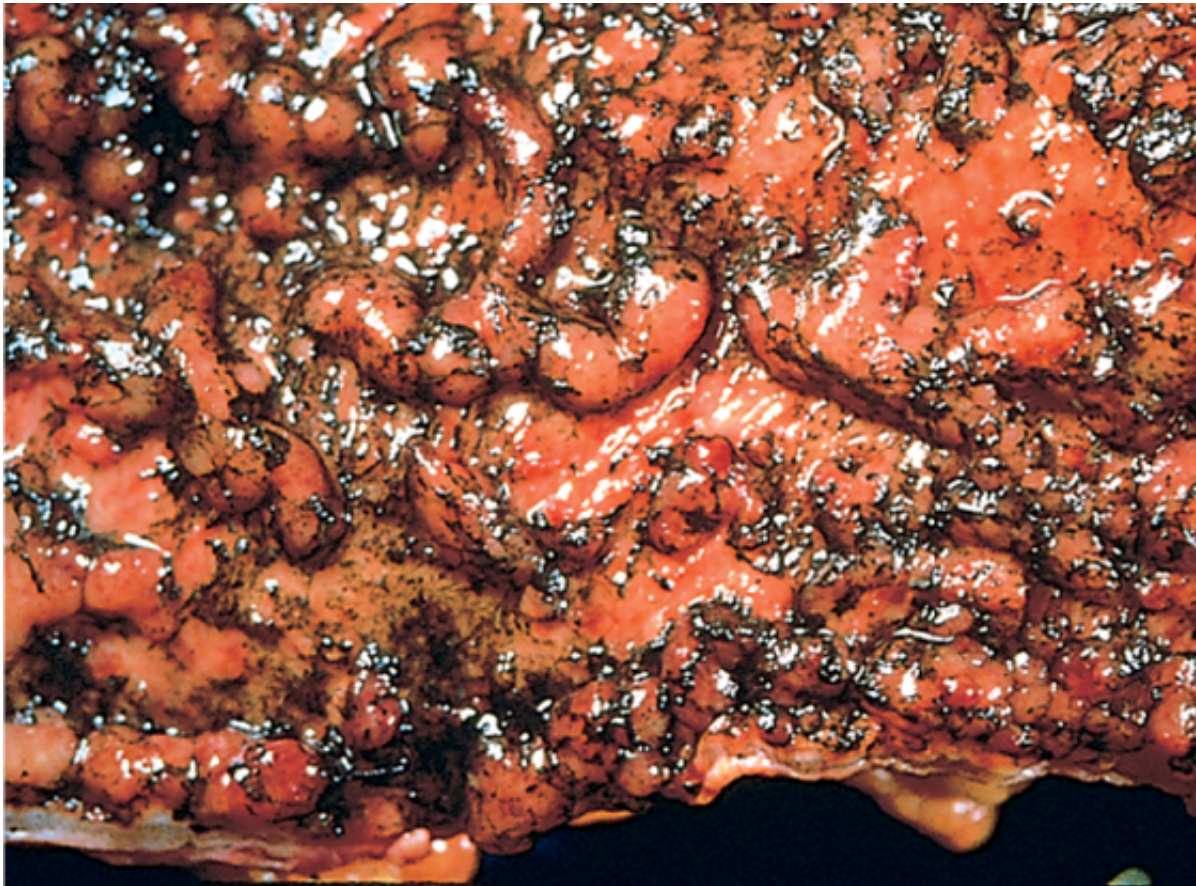
\*Not all features present in a single case.

†Crohn disease can occur elsewhere in the small intestine as well.

‡Based on likelihood of disease recurrence after surgical removal of a diseased segment.

Ulcerative colitis is somewhat more common than Crohn disease in the United States and Western Europe per 100,000 population, but it is infrequent in Asia, Africa, and South America. As with Crohn disease, its incidence has risen in recent decades. In the United States it is more common among whites than among nonwhites. There is a familial predilection. The disease may arise at any age, with a peak incidence between ages 20 and 25 years. There is a strong association; about 20% of persons with the disorder have affected relatives. Individuals with ulcerative colitis have an increased frequency of the *HLA-B27* allele, but this association is related to the spondylitis





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Figure 15-33 Ulcerative colitis. The pale, irregular regions comprise ulcerations that have in many instances coalesced. The tendency toward pseudopolyp formation is already evident. The darker material is adherent

### Morphology

**Ulcerative colitis involves the rectum and sigmoid and may involve the entire colon. With an even higher proximal extension (pancolitis) occurs much less frequently. The disease involvement is continuous from the distal colon, so that skip lesions are not seen. The disease denotes ongoing inflammatory destruction of the mucosa, with macroscopic granularity with friability and easy bleeding. With severe active disease, there is extensive ulceration of the mucosa in the distal colon or throughout its length (Fig. 15-33). Ischemic regenerating mucosa bulge upward to create **pseudopolyps**. Often the undermined mucosal islands interconnect to create tunnels covered by tenuous mucosal bridges. As with Crohn disease, ulcerative colitis are frequently aligned along the axis of the colon, but rarely do the serpentine ulcers of Crohn disease. In rare cases, the muscularis propria is so completely destroyed that perforation and pericolic abscess formation. Exposure of the muscularis propria material also may lead to complete shutdown of neuromuscular function. When this occurs, the colon progressively swells and becomes gangrenous (**toxic megacolon**). With indolent or healing of active disease, progressive mucosal atrophy leads to a flattened and atrophic**

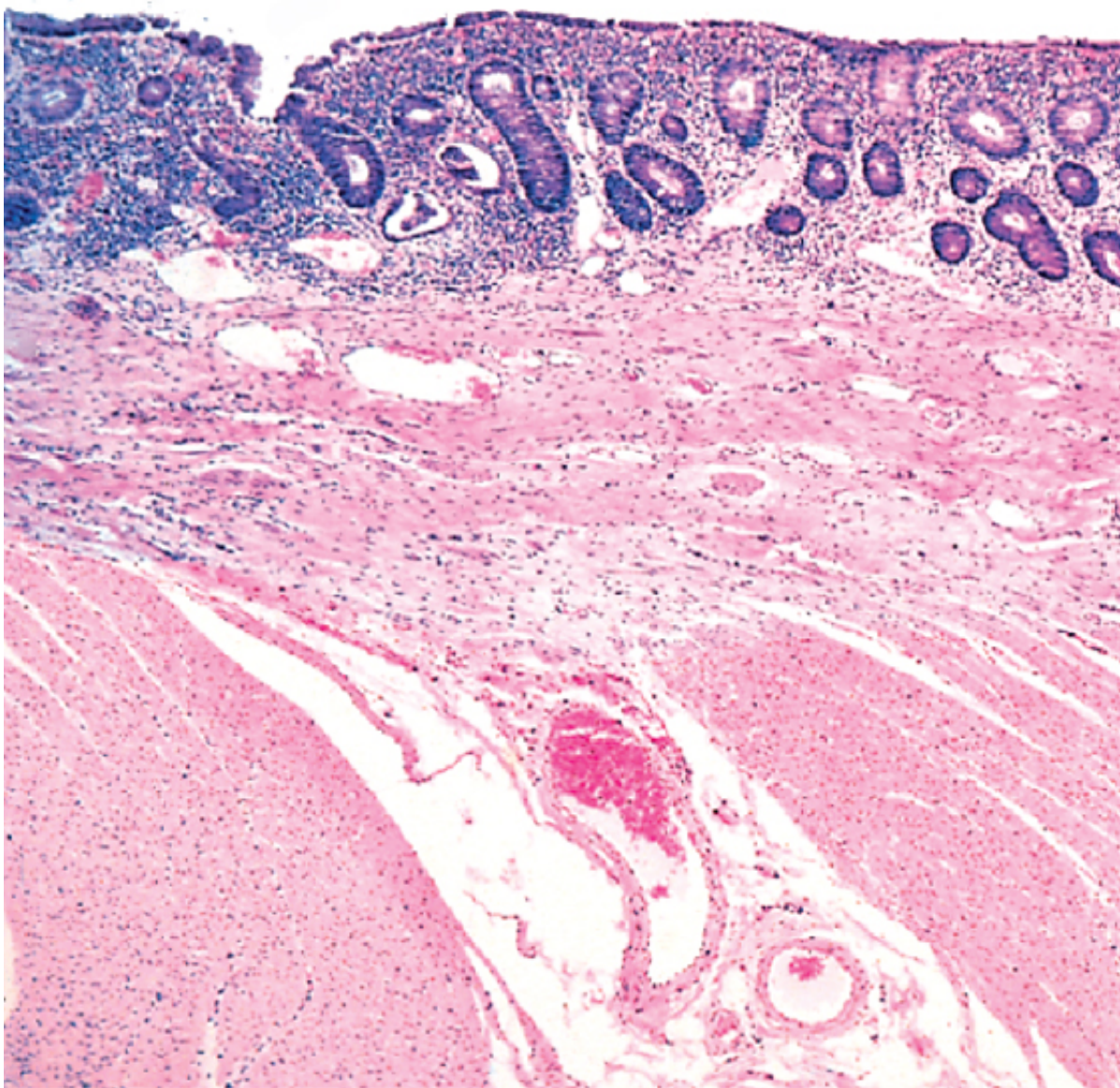
The pathologic features of ulcerative colitis are those of mucosal inflammation, ulceration, and mucosal damage (Fig. 15-34).

**A diffuse, predominantly mononuclear inflammatory infiltrate in the lamina propria is universally present, even at the time of clinical presentation. Neutrophilic infiltration of the crypts may produce collections of neutrophils in crypt lumina (**crypt abscesses**).**



for ulcerative colitis and may be observed in Crohn disease or any active inflammatory bowel disease. In Crohn disease, there are no granulomas, although rupture of crypt abscesses may elicit a foreign body reaction in the lamina propria. **Further destruction of the mucosa leads to ulceration** extending into the submucosa and sometimes leaving only the raw, exposed surface. In remission of active disease, **granulation tissue fills in the ulcer craters**, forming a new layer of the mucosal epithelium. **Submucosal fibrosis and mucosal architectural changes remain as residua of healed disease.**

The most serious complication of ulcerative colitis is the development of colon cancer. Factors that govern the risk: duration of the disease and its anatomic extent. It is believed that if the disease is limited to the left colon the risk is minimal, and at 20 years the risk is on the order of 1%. If the risk of carcinoma is 10% at 20 years and 15% to 25% by 30 years. Overall, the annual risk of cancer in persons with ulcerative colitis of more than 10 years' duration is 0.8% to 1.0%.



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Figure 15-34 Ulcerative colitis. Low-power micrograph showing marked chronic inflammation of the mucosa with a  
fibrosis, and a normal muscle wall.



### *Clinical Features*

Ulcerative colitis is a chronic relapsing disorder marked by attacks of bloody mucoid diarrhea that and then subside, only to recur after an asymptomatic interval of months to years or even decade cramps, tenesmus, and colicky lower abdominal pain that is relieved by defecation. Some people bloody stools are more common with ulcerative colitis than with Crohn disease, and the blood loss person the first attack is the last, representing about 10% of patients. At the other end of the spec to such serious bleeding and fluid and electrolyte imbalance as to constitute a medical emergency majority of individuals with ulcerative colitis experience a relapsing course. Concurrent infections, may first bring ulcerative colitis to light; they do not precipitate the disease.

*Extra-intestinal manifestations, particularly migratory polyarthritis, are more common with ulcerativ* Uncommon but *life-threatening complications* include severe diarrhea and electrolyte derangement dilation (toxic megacolon) with potential rupture, and perforation with peritonitis. Inflammatory stric uncommon, must be differentiated from cancer.

Diagnosis can usually be made by endoscopic examination and biopsy. Specific infectious causes feared long-term complication of ulcerative colitis is cancer. The sequential mucosal changes from the rationale for surveillance programs of repeated colonoscopies and multiple biopsies aimed at prophylactic colectomy. Since the carcinomas that develop from ulcerative colitis are frequently of major importance. DNA damage with microsatellite instability has been detected in ulcerative colit type of damage was also found in nondysplastic areas of the gut of persons with ulcerative colitis, DNA repair defects in mucosal cells throughout the intestine.

### **SUMMARY**

**Inflammatory Bowel Disease (IBD)** Crohn disease and ulcerative colitis are bowel diseases believed to result from abnormal local immune responses a and/or self antigens in the intestine. *Crohn disease:*

Associated with HLA-DR7 and -DQ4 alleles, and with mutations in th encodes an intracellular sensor of microbes Results from a chronic T inflammatory reaction involving IFN- $\gamma$ -producing T<sub>H</sub>1 cells and, perha cells Manifested by chronic inflammation with granulomas, ulcers, an fibrosis, involving the terminal ileum and colon Consequences include abdominal abscesses, intestinal obstruction, and increased risk of ca

*Ulcerative colitis:*

Associated with HLA-DRB1 Manifested by superficial ulcers in the co extensive fibrosis; the nature of the pathologic immune response is u complication is the increased risk of carcinoma.





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## TUMORS OF THE SMALL AND LARGE INTESTINES

Epithelial tumors of the intestines are a major cause of morbidity and mortality worldwide. The colon is the primary site for neoplasms than any other organ in the body. Colorectal cancer ranks second only to bronchogenic carcinoma as a cause of cancer death in the United States. About 5% of Americans will develop colorectal cancer, and 40% of this cancer will be fatal. Adenocarcinomas constitute the vast majority of colorectal cancers and represent 70% of all malignant tumors of the gastrointestinal tract. Curiously, the small intestine is an uncommon site for benign or malignant tumors despite its large mucosal surface area. The classification of intestinal tumors is the same for the small and large bowel (Table 15-11).

Before embarking on our discussion, several concepts pertaining to terminology must be emphasized.

A *polyp* is a mass that protrudes into the lumen of the gut; traction on the mass may create a stalk. Alternatively, the polyp may be *sessile*, without a definable stalk. Polyps may be formed as a result of hyperplasia, inflammation, or architectural distortion. These polyps are *non-neoplastic* and do not have malignant potential. Polyps that arise as the result of epithelial proliferation and dysplasia are termed *adenomatous polyps* and are precursors of carcinoma. *Hyperplastic polyps* are the most common polyps; they do not have malignant potential. However a lesion known as *sessile serrated adenoma* or *hyperplastic polyp*, may have malignant potential (discussed below).

Table 15-11. Tumors of the Small and Large Intestines

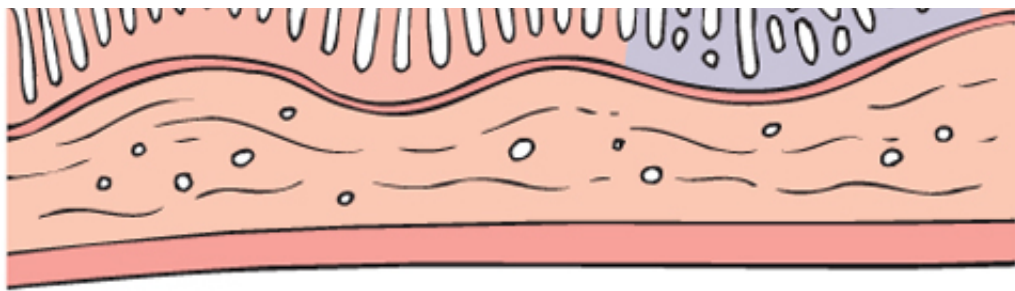
<b>Non-neoplastic Polyps</b>
Hyperplastic polyps
Hamartomatous polyps
Juvenile polyps
Peutz-Jeghers polyps
Inflammatory polyps
Lymphoid polyps
<b>Neoplastic Epithelial Lesions</b>
Benign polyps
Adenomas
Malignant lesions
Adenocarcinoma
Squamous cell carcinoma of the anus
<b>Other Tumors</b>
Gastrointestinal stromal tumors
Carcinoid tumor
Lymphoma

### SESSILE POLYPS

#### Hyperplastic polyp

#### Adenoma

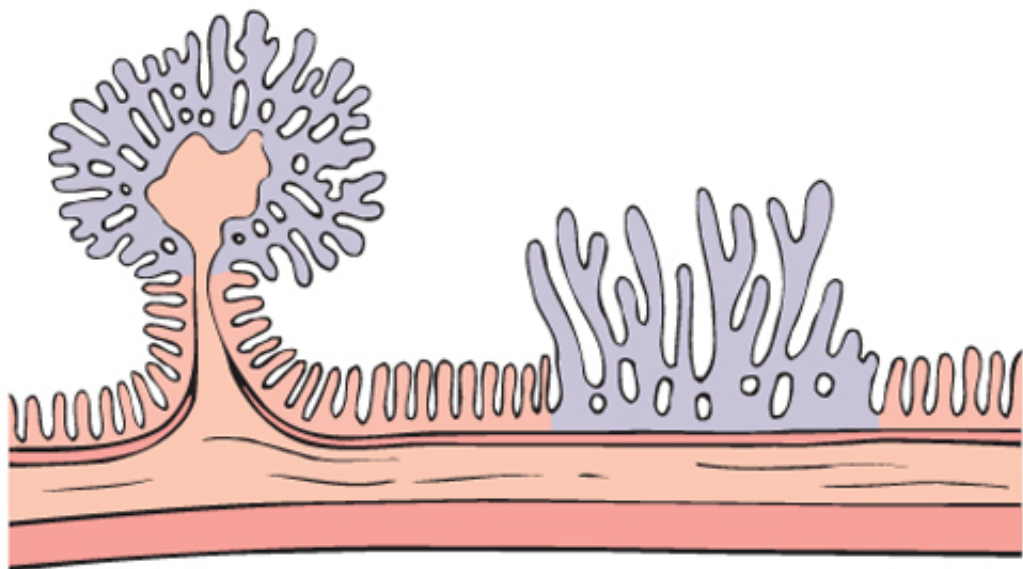




## ADENOMAS

### Pedunculated Tubular

### Sessile Villous



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Figure 15-35 Two forms of sessile polyp (hyperplastic polyp and adenoma) and of two types of adenoma (ped association between the tubular architecture for pedunculated adenomas and the villous arch

Some polypoid lesions may be caused by submucosal or mural tumors. However, as with the stor specified, refers to lesions arising from the epithelium of the mucosa.

### Non-Neoplastic Polyps

The overwhelming majority of intestinal polyps occur sporadically, particularly in the colon, and in neoplastic polyps represent about 90% of all epithelial polyps in the large intestine and are found years or older. Most are *hyperplastic polyps*, which are small (<5 mm in diameter), nipple-like, her mucosa. They may occur singly but are more often multiple. Although they may be anywhere in th rectosigmoid region. Histologically, they contain abundant crypts lined by well-differentiated goble by a scant lamina propria. Although the vast majority of hyperplastic polyps have *no malignant po* some "hyperplastic polyps," the so-called sessile serrated adenomas, located on the right side of carcinomas. They may be solitary or multiple ("hyperplastic polyposis"). As discussed later, these can give rise to colon cancers by the mismatch repair pathway.

*Juvenile polyps* are essentially hamartomatous proliferations, mainly of the lamina propria, enclosed by normal mucosa. They occur most frequently in children younger than 5 years old but also are found in adults of all ages. They are called *retention polyps*. Irrespective of terminology, the lesions are usually large in children (1-3 cm), are rounded, smooth, or slightly lobulated and sometimes have a stalk as long as 2 cm. In general, being hamartomatous they have no malignant potential. Juvenile polyps may be the source of rectal bleeding, twisted on their stalks to undergo painful infarction.

Polyps that develop in the Peutz-Jegher syndrome are discussed in the later section on Familial FAP.

## Adenomas

Adenomas are neoplastic polyps that range from small, often pedunculated, tumors to large lesions. The incidence of adenomas in the small intestine is very low, this discussion focuses on those adenomas in the colon. The prevalence of colonic adenomas is 20% to 30% before age 40, rising to 40% to 50% after age 60. There is a well-defined familial predisposition to sporadic adenomas, accounting for about a fourfold increase in first-degree relatives, and also a fourfold greater risk of colorectal carcinoma in any person with adenomatous polyps.

*All adenomatous lesions arise as the result of epithelial proliferation and dysplasia, which may progress to carcinoma.* Furthermore, there is strong evidence that most sporadic invasive colorectal carcinomas arise from preexisting adenomatous lesions. Adenomatous polyps are segregated into four subtypes on the basis of histology:

*Tubular adenomas*-mostly tubular glands, recapitulating mucosal topology  
*Villous adenomas*-villous architecture  
*Tubulovillous adenomas*-a mixture of the above  
*Sessile serrated adenomas*-serrated epithelium lining the crypts

Tubular adenomas are by far the most common; 5% to 10% of adenomas are tubulovillous, and 1% to 5% are villous. Most adenomas are small and pedunculated; villous adenomas tend to be large and sessile. Conversely, large sessile polyps usually show villous features.

The malignant risk with an adenomatous polyp is correlated with three interdependent features: polyp size, polyp histology, and severity of epithelial dysplasia-as follows:

Cancer is rare in tubular adenomas smaller than 1 cm in diameter. The likelihood of cancer increases with the size of the adenoma. Villous adenomas larger than 4 cm in diameter. Severe dysplasia, when present, is often found in villous adenomas. The *maximum diameter is the chief determinant of the risk of an adenoma's harboring cancer*. The size of the adenoma, the histology, and the severity of dysplasia provide substantive independent information.

## Morphology

**Tubular adenomas** may arise anywhere in the colon, but about half are found in the right colon, the proportion increasing with age. In about half of the instances they occur singly, but more lesions are distributed at random. The smallest adenomas are sessile; lesions larger than 1 cm are usually pedunculated and identified at endoscopy. Among the larger tubular adenomas up to 2.5 cm in diameter, the stalks are 1 to 2 cm long and have raspberry-like heads (Fig. 15-36A). Histologically the stalk is composed of normal colonic mucosa, but the head is composed of neoplastic epithelium, forming branched villi. The cells are hyperchromatic, somewhat disorderly, which may or may not show mucin secretion. In some instances there are small foci of villous architecture. In the clearly benign lesions, the villi are well separated by lamina propria, and the level of dysplasia or cytologic atypia is low. In more advanced lesions, degrees of dysplasia may be encountered, ranging up to cancer confined to the mucosa (**carcinoma in situ**) or **invasive carcinoma** extending into the submucosa of the stalk. A few adenomas show only superficial erosion of the epithelium, the result of mechanical trauma.

**Villous adenomas** are the larger and more ominous of the epithelial polyps. They are found in all parts of the colon, most commonly in the rectum and rectosigmoid, but they may be located anywhere. They are sessile, up to 10 cm in diameter, velvety or cauliflower-like masses projecting from the surrounding normal mucosa. The histology is that of frondlike villiform extensions of the mucosa. The villi are composed of dysplastic, sometimes very disorderly, sometimes piled-up, columnar epithelium (Fig. 15-36B). In some instances, degrees of dysplasia may be encountered, and invasive carcinoma is found in as many as 40% of the lesions.



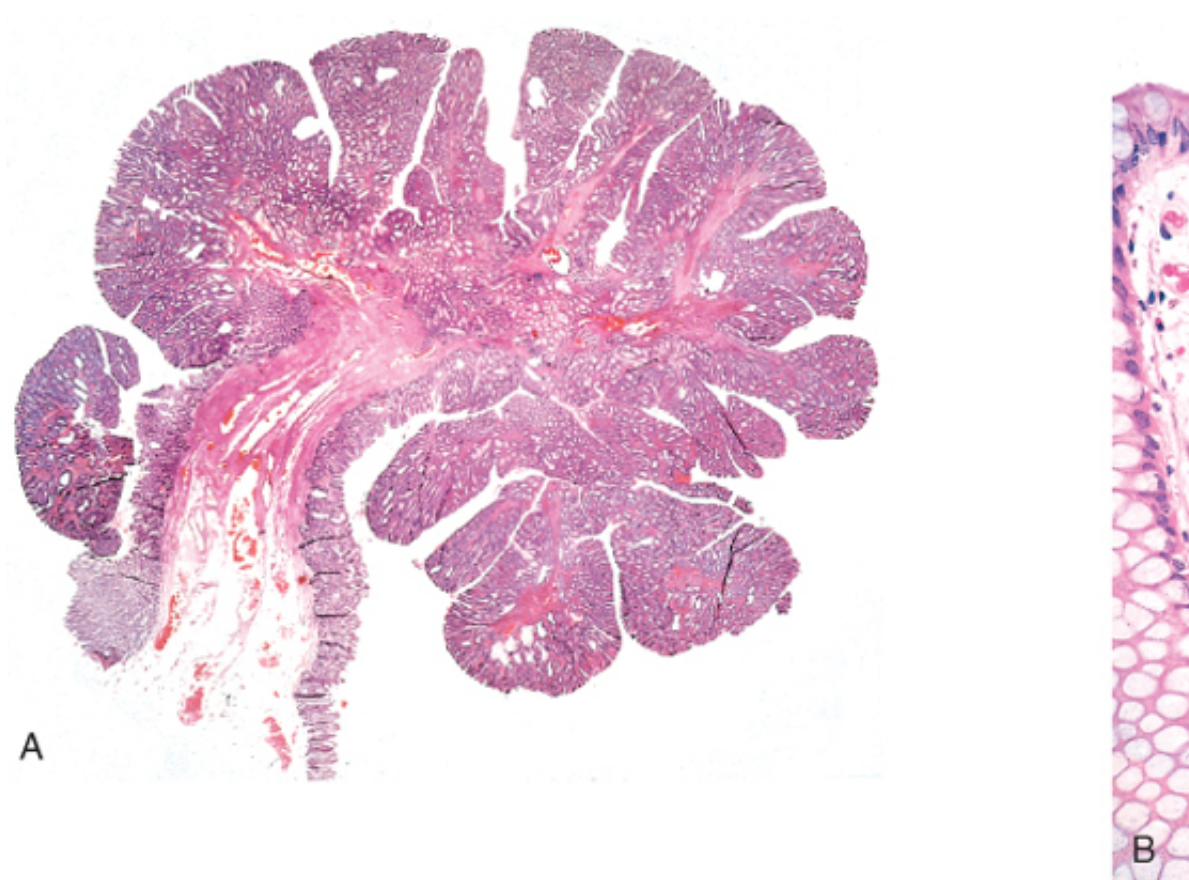
frequency being correlated with the size of the polyp.

**Tubulovillous adenomas** are composed of a broad mix of tubular and villous areas between the tubular and the villous lesions in their frequency of having a stalk or broad base, degree of dysplasia, and the risk of harboring intramucosal or invasive carcinoma.

### Clinical Features

The smaller adenomas are usually asymptomatic, until such time that occult bleeding leads to clinical symptoms. Larger adenomas are much more frequently symptomatic because of overt or occult rectal bleeding. They do not secrete sufficient amounts of mucoid material rich in protein and potassium to produce hypoprotei- nemia. Adenomas, regardless of their location in the alimentary tract, are to be considered potentially malignant and adequate excision is mandated.

### Familial Polyposis Syndromes



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Figure 15-36 **A**, Pedunculated adenoma showing a fibrovascular stalk covered by normal colonic mucosa and a h  
glands-hence the blue color. **B**, A small focus of adenomatous epithelium in an otherwise normal (mucin-secre  
dysplastic columnar epithelium (deeply stained) can populate a colonic crypt ("tubu

Familial polyposis syndromes are uncommon autosomal dominant disorders. Their importance lies in the transformation and in the insights that such transformation has provided in unraveling the molecular basis of cancer. Patients with *familial adenomatous polyposis* (FAP) typically develop 500 to 2500 colonic adenomas that a minimum number of 100 is required for the diagnosis. Multiple adenomas may also be present elsewhere in the gastrointestinal tract. The risk of colonic cancer is virtually 100% if prophylactic colectomy is not performed. The genetic defect underlying FAP has been localized to the

polyposis syndrome is permanent and genetic, whereas sporadic polyposis has been related to the discussed below; *Gardner syndrome* and the much rarer *Turcot syndrome* seem to share the same genetic basis. These syndromes differ from FAP with respect to the occurrence of extra-intestinal tumors in the latter two syndromes, to name a few.

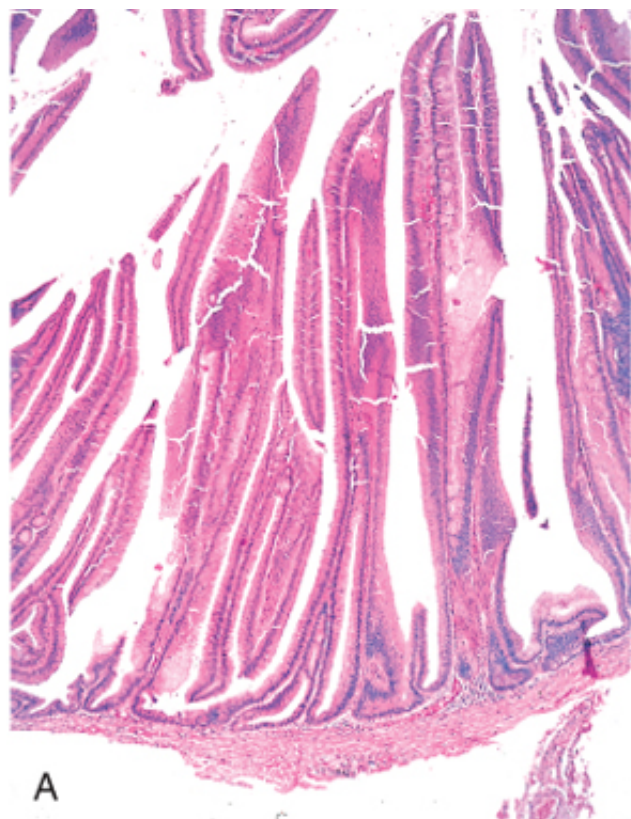
*Peutz-Jeghers* polyps are uncommon hamartomatous polyps that occur as part of the rare autosomal recessive syndrome characterized in addition by melanotic mucosal and cutaneous pigmentation. This syndrome is caused by a mutation in the *SMAD4* gene, which encodes a serine threonine kinase. *Cowden syndrome* is also characterized by hamartomatous polyps of the gastrointestinal tract and by an increased risk of neoplasms of the thyroid, breast, uterus, and skin. This syndrome is caused by a mutation in the *PTEN* (phosphatase and tensin homologue) tumor suppressor gene. This gene, mutated in a large number of human cancers, has the ability to regulate many intracellular signaling pathways. It acts as a growth inhibitor by antagonizing several tyrosine kinase receptors (e.g., epidermal growth factor receptor) and by favoring apoptosis. *Peutz-Jeghers* and *Cowden* syndromes, like the other familial polyposis syndromes, are associated with an increased risk of colorectal and extraintestinal malignancies.

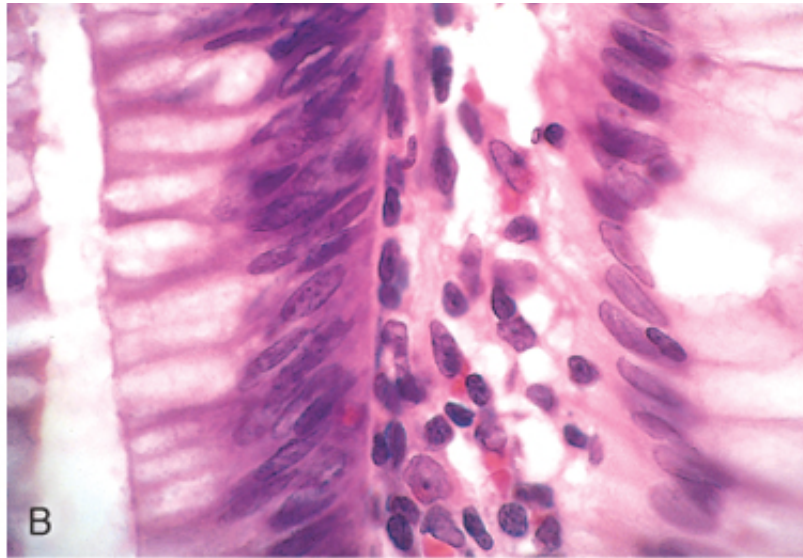
## Colorectal Carcinoma

A great majority (98%) of all cancers in the large intestine are adenocarcinomas. They represent a major cause of death in the medical profession, because they almost always arise in adenomatous polyps that are generally considered precursors. With about 134,000 new cases per year and about 55,000 deaths, this disease accounts for nearly 15% of all cancer deaths in the United States.

### Epidemiology

The peak incidence for colorectal cancer is 60 to 70 years of age; fewer than 20% of cases occur in children. The adenoma-carcinoma sequence is the presumed precursor lesion for most of the tumors; the frequency with which colorectal carcinoma arises in the absence of adenomas remains undefined but appears to be low. Males are affected about 20% more often than females.





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Figure 15-37 **A**, Sessile adenoma with villous architecture. Each frond is lined by dysplastic epithelium. **B**, Port  
epithelium on the left and normal colonic columnar epithelium on the r

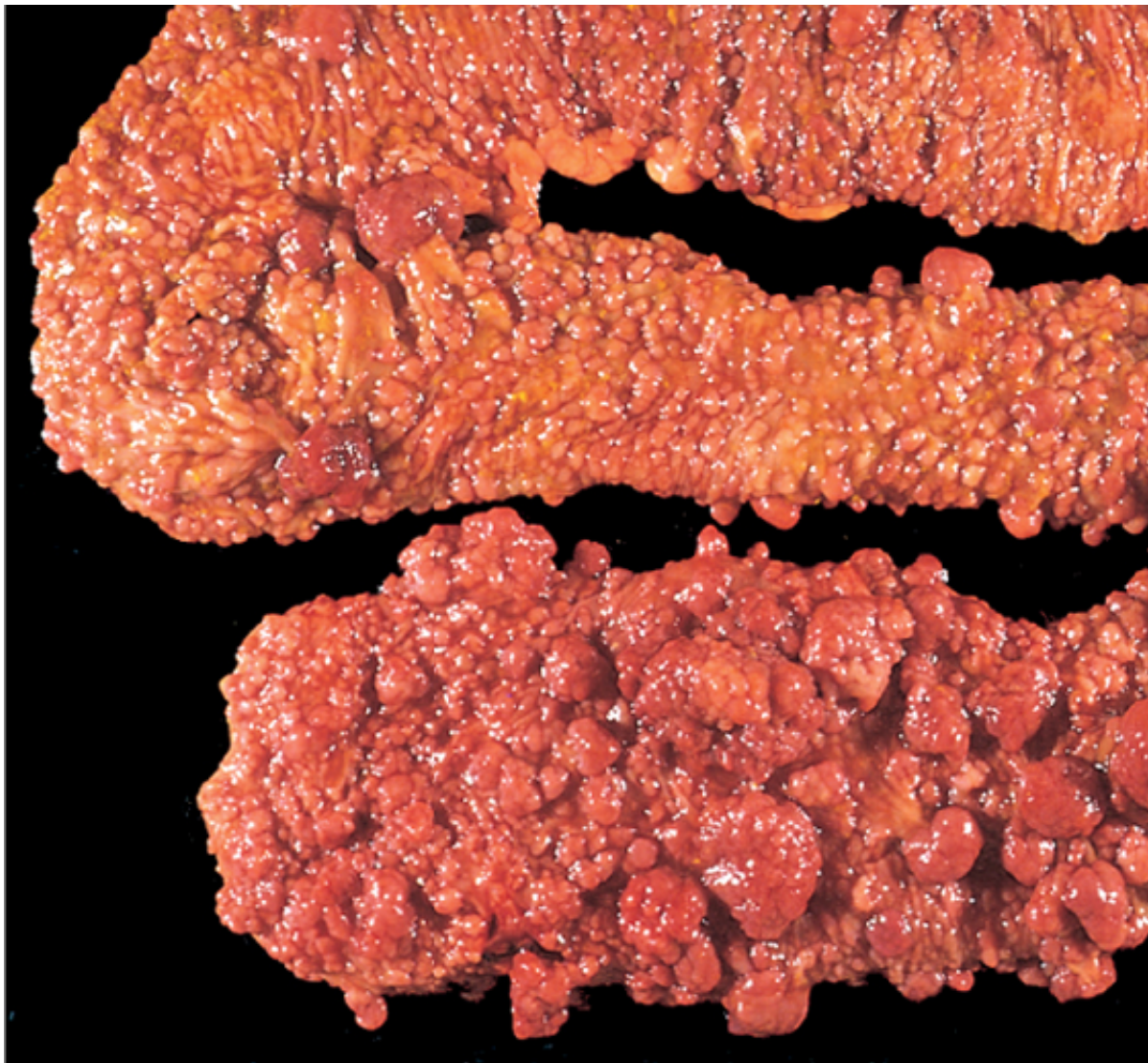
Both genetic and environmental influences contribute to the development of colorectal cancers. In a person, preexisting ulcerative colitis or one of the polyposis syndromes must be suspected. In addition, *nonpolyposis colorectal cancer syndrome* (HNPCC, also known as Lynch syndrome), caused by defects in DNA repair genes, are at a high risk of developing colorectal cancers. (HNPCC patients are also at risk for cholangiocarcinomas.)

Colorectal carcinoma has a worldwide distribution, with the highest incidence rates in the United States, Denmark, Sweden, and other developed countries. Its incidence is substantially lower, up to 30-fold lower, in Africa. The incidence in Japan, which formerly was very low, has now risen to the intermediate level. Environmental influences, particularly dietary practices, are implicated in the striking geographic variation. Factors receiving the most attention are (1) a low content of unabsorbable vegetable fiber, (2) a corresponding high intake of carbohydrates, (3) a high fat content (as from meat), and (4) decreased intake of protective micronutrients. It is theorized that reduced fiber content leads to decreased stool bulk, increased fecal retention in the large intestine. Potentially toxic oxidative byproducts of carbohydrate degradation by bacteria are thought to be present in the stool and are held in contact with the colonic mucosa for longer periods of time. Moreover, increased levels of cholesterol and bile acids by the liver, which in turn may be converted into potential carcinogens by the colon, are thought to contribute. Diets containing less of vitamins A, C, and E, which may act as oxygen radical scavengers. Intriguing as this hypothesis is, it remains unproven.

Several recent epidemiologic studies suggest that use of [aspirin](#) and other NSAIDs exerts a protective effect against colorectal cancer. In the Nurses' Health Study, women who used four to six tablets of [aspirin](#) per day for 10 years or more had a 50% reduction in risk of colorectal cancer. It is suspected that this effect is via inhibition of cyclooxygenase-2 (COX-2). This enzyme promotes carcinogenesis in 40% to 90% of adenomas. How COX-2 promotes carcinogenesis is not clear. Some studies suggest that COX-2 promotes production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), which seems to favor epithelial cell proliferation, inhibit apoptosis, and promote angiogenesis by enhancing production of vascular endothelial growth factor.







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 Figure 15-38 Familial adenomatous polyposis. The surface is carpeted by innumerable polypoid adenomas. (Court Hospital, Boston, Massachusetts.)

The development of carcinoma from adenomatous lesions is documented by these general obser

Populations that have a high prevalence of adenomas have a high prevalence of colorecta  
 of adenomas within the colorectum is more or less comparable to that of colorectal cancer.  
 polyps antedates by some years the peak for colorectal cancer. When invasive carcinoma i  
 adenomatous tissue is often present. The risk of cancer is directly related to the number of  
 certainty of cancer in persons with familial polyposis syndromes. Programs that assiduously  
 adenomas, and remove all that are identified, reduce the incidence of colorectal cancer.

Table 15-12. Molecular Genetic Pathways of Colorectal Cartinogenesis

Molecular Pathway	Hereditary Colorectal Carcinoma			Sporadic
	Clinical Phenotype	Histopathology	Genetics	Clinical Phenotype



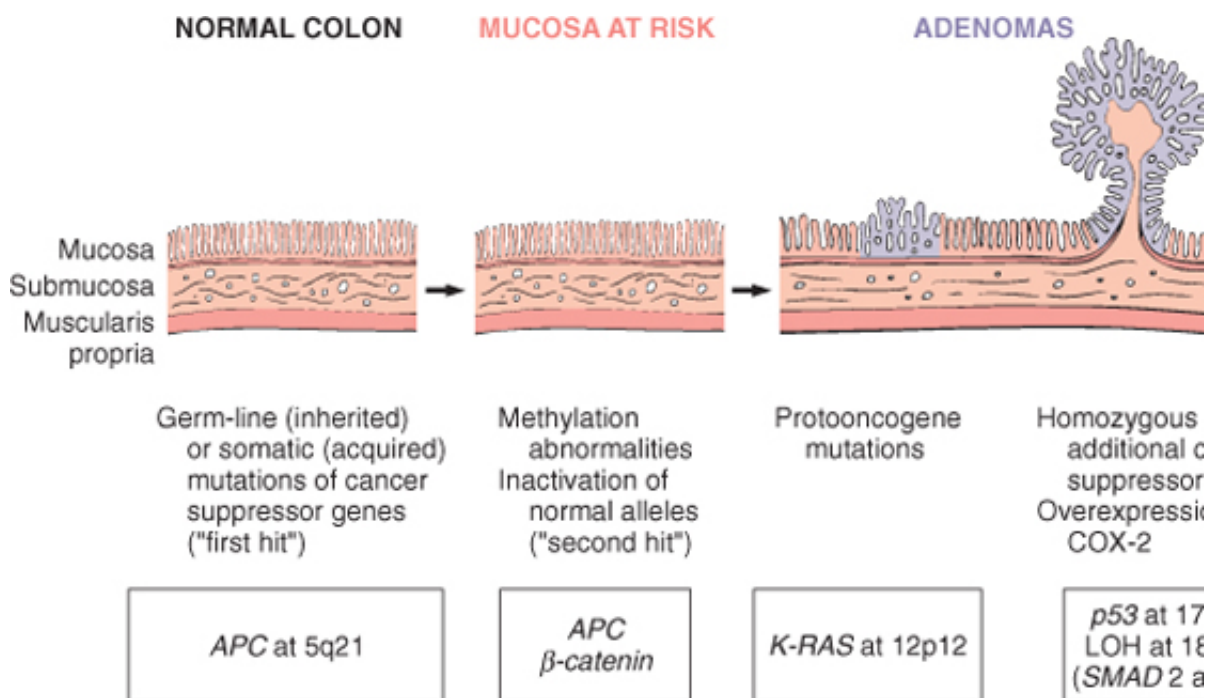
Adenocarcinoma sequence	Familial adenomatous polyposis	Innumerable adenomatous polyps Moderately differentiated adenocarcinomas	Germ-line <i>APC</i> inactivation	Left-sided predominant cancers
Microsatellite instability	Hereditary nonpolyposis colorectal cancer	Mucinous and poorly differentiated carcinomas with lymphocytic infiltrates	Germ-line inactivation of <i>MLH1</i> or <i>MSH2</i> DNA repair genes	Right-sided predominant cancers

\*Genes encoding APC/ $\beta$ -catenin, K-RAS, SMADS, p53. Adapted from Iacobuzio-Donahue CA, Montgomery EA: Gastrointestinal a

### Colorectal Carcinogenesis

Study of colorectal carcinogenesis has provided fundamental insights into the general mechanism principles were discussed in [Chapter 6](#). Here we will discuss concepts specifically pertinent to car

It is now believed that *there are two pathogenetically distinct pathways for the development of col the adenoma-carcinoma sequence), and the mismatch repair (or microsatellite instability) pathway* involve the stepwise accumulation of multiple mutations, but the genes involved and the mechanis are different.



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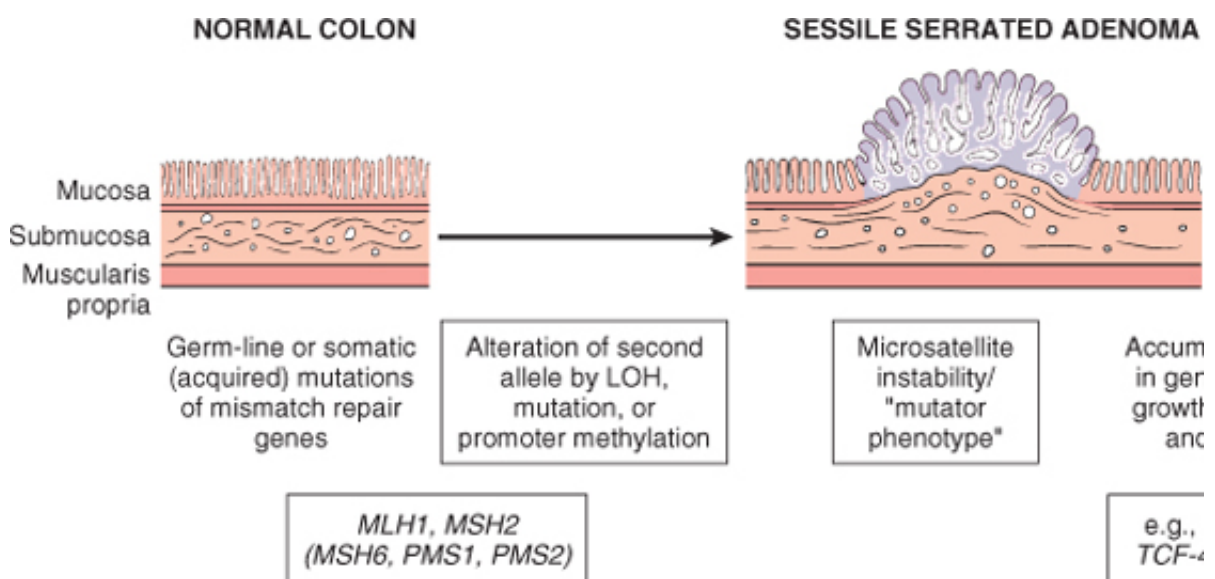
Figure 15-39 Morphologic and molecular changes in the adenoma-carcinoma sequence. It is postulated that loss of *APC* occurs early. Individuals may be born with one mutant allele, making them extremely prone to develop colon cancer. This is the "first hit" according to Knudson's hypothesis ([Chapter 6](#)). The loss of the intact copy of *APC* follows *K-RAS*, losses at 18q21 involving *SMAD2* and *SMAD4*, and the inactivation of the tumor suppressor gene *p53*, i.e., additional mutations occur. Although there seems to be a temporal sequence of changes, the accumulation of mutations in a certain order, seems to be critical.

The first pathway, variously called the *adenoma-carcinoma sequence*, the *APC/ $\beta$ -catenin pathway*, is characterized by chromosomal instability associated with stepwise accumulation of mutations in

suppressor genes. The molecular evolution of colon cancer along this pathway occurs through a series of stages (Fig. 15-39). Initially, there is localized epithelial proliferation. This is followed by the formation of adenomas, which may or may not enlarge, become more dysplastic, and ultimately develop into invasive cancers. Such adenoma-carcinoma sequence accounts for 80% of sporadic colon tumors. The genetic correlates of this pathway are as follows:

**Loss of the APC tumor suppressor gene.** This is believed to be the earliest event in the formation of colon cancer. In FAP and Gardner syndromes, germ-line mutations in the *APC* gene give rise to hundreds of adenomas. Both copies of the *APC* gene must be lost for adenomas to develop. As discussed in Chapter 6, the *APC* protein is intimately linked to  $\beta$ -catenin. Normal APC promotes the degradation of  $\beta$ -catenin. When APC is lost, accumulated  $\beta$ -catenin translocates to the nucleus and activates the transcription of several genes which promote cell proliferation. *APC* mutations are present in 60% to 80% of sporadic colon cancers. ***RAS* gene.** The *RAS* gene encodes a signal transduction molecule that oscillates between an activated guanine nucleotide-bound state and an inactive guanosine diphosphate-bound state. As discussed in Chapter 6, mutated *RAS* is constitutively active and prevents apoptosis. *K-RAS* is mutated in fewer than 10% of adenomas smaller than 1 cm, and in 50% of carcinomas. ***18q21 deletion.*** Loss of a putative cancer suppressor gene located on chromosome 18q21. Three genes have been mapped to this chromosome location: *SMAD2*, and *SMAD4*. The *SMAD* genes are considered to be the most relevant ones for components of the transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway. Because TGF- $\beta$  inhibits cell growth, the loss of these genes may allow unrestrained cell growth. **Loss of *p53*.** Loss of this gene is found in 60% to 80% of colon cancers, yet similar losses are infrequent in adenomas, suggesting that mutations in *p53* are critical for carcinogenesis. The critical role of *p53* in cell cycle regulation was discussed in Chapter 6.

In addition to these changes, alterations in the methylation level of tumor suppressor genes occur in the adenoma-carcinoma pathway.



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Figure 15-40 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair lead to microsatellite instability and permit the accumulation of mutations in numerous genes. If these mutations affect genes involved in cell growth, the tumor may develop.

The second pathway of colorectal carcinogenesis is characterized by genetic lesions in *DNA mismatch repair* genes. This pathway is involved in 10% to 15% of sporadic cases. As in the *APC*/ $\beta$ -catenin schema, there is accumulation of mutations in a series of genes. There may be no detectable antecedent lesions, or the tumors may develop from sessile serrated adenomas. Inactivation of DNA mismatch repair genes is the fundamental and the most likely initiating event in this pathway. Inherited mutations in one of five DNA mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, *PMS1*, and *PMS2*) are found in familial adenomatous polyposis (FAP) and in the

the hereditary nonpolyposis colon carcinoma (HNPCC). Of these, *MLH1* and *MSH2* are the ones derived and sporadic colon carcinomas with DNA mismatch repair gene defects. Loss of DNA mismatch repair leads to a hypermutable state in which simple repetitive DNA sequences, called *microsatellites*, are unstable and undergo widespread alterations in these repeats. The resulting *microsatellite instability* (MSI) is the molecular hallmark of the defect in DNA repair, and hence this pathway is often referred to as the MSI pathway. Because of the multiple mutations in noncoding regions of the genes. However, some microsatellite sequences are located in the coding regions of genes that regulate cell growth. Such genes include type II TGF- $\beta$  receptor and *BAX*. TGF- $\beta$  signaling inhibits cell growth and the *BAX* gene product causes apoptosis. Loss of mismatch repair leads to the accumulation of mutations in these genes, culminating in the emergence of colorectal carcinomas.

Although there is no readily identifiable adenoma-carcinoma sequence that typifies tumors arising from the MSI pathway, it has been noted that sessile serrated adenomas located on the right side of the colon display MSI and that tumors that arise via the mismatch repair pathway do show some distinctive morphologic features such as mucinous histology, and infiltration by lymphocytes. In general, these tumors have a better prognosis than those that arise by the *APC*/ $\beta$ -catenin pathway.

A note of caution is needed in the evaluation of the molecular changes discussed in the adenoma-carcinoma sequence. None of the changes listed appears universally. For instance, defects in *APC* are found in dysplastic polyps associated with sporadic colorectal cancer. In fact, the sequence of gene alterations in hereditary colon cancer may not be as evident in sporadic tumors. Most likely, the accumulation of mutations occurs in a different order than the order of their appearance.







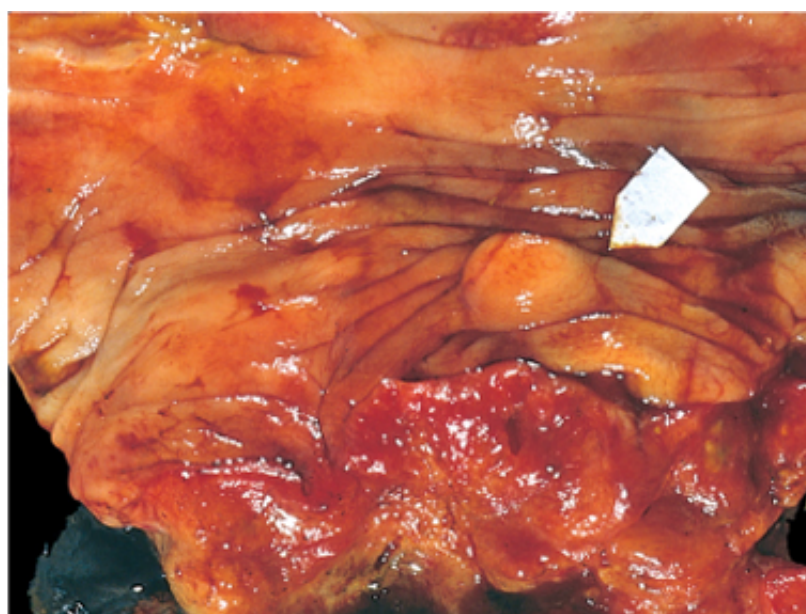
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 Figure 15-41 Carcinoma of the cecum. The exophytic carcinoma projects into the lumen but l

### Morphology

About 25% of colorectal carcinomas are in the cecum or ascending colon, with a si rectum and distal sigmoid. An additional 25% are in the descending colon and pro remainder are scattered elsewhere. Hence, a substantial portion of cancers is undi proctosigmoidoscopic examination. Most often carcinomas occur singly and have f adenomatous origins. When multiple carcinomas are present, they are often at wid colon.

Although all colorectal carcinomas begin as in situ lesions, they evolve into differer **Tumors in the proximal colon tend to grow as polypoid, exophytic masses th of the capacious cecum and ascending colon (Fig. 15-41).** Obstruction is uncor **in the distal colon are discovered, they tend to be annular, encircling lesions napkin-ring constrictions of the bowel and narrowing of the lumen (Fig. 15-42** napkin ring are classically heaped up. Both forms of neoplasm directly penetrate th course of time (probably years) and may appear as firm masses on the serosal sur

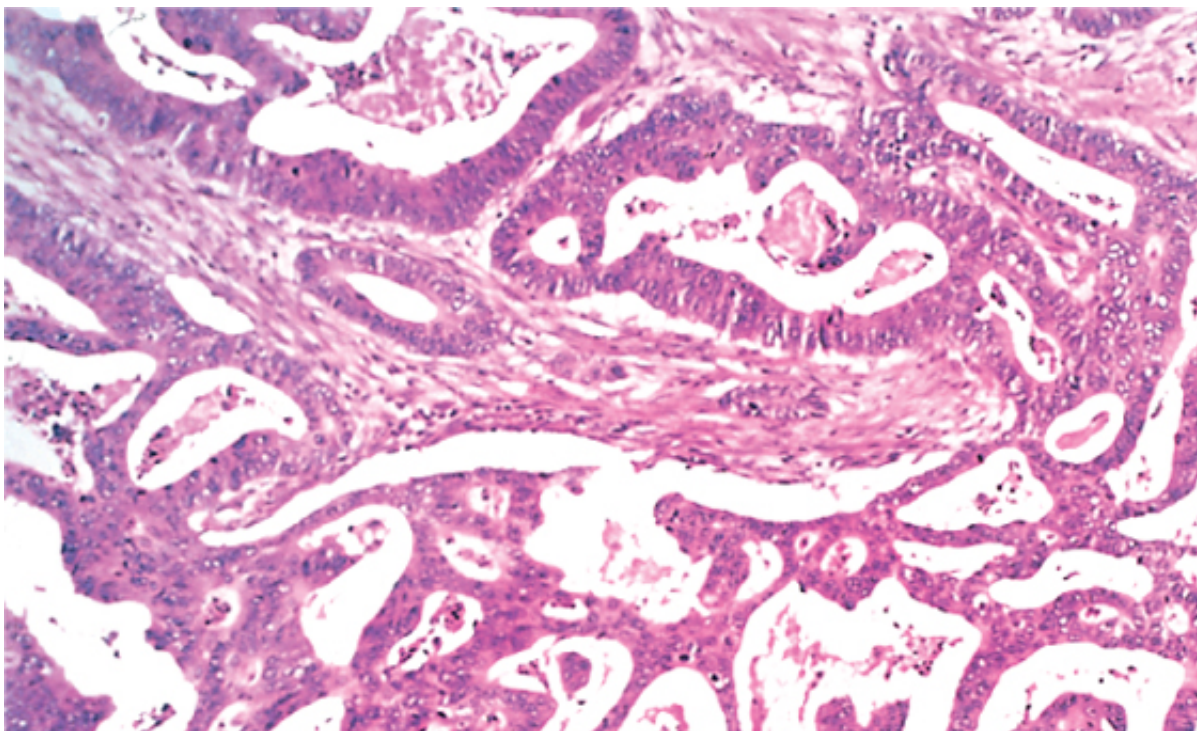
Regardless of their gross appearance, all colon carcinomas are microscopically sir adenocarcinomas that range from well-differentiated (Fig. 15-43) to undifferentiated masses. Many tumors produce mucin, which is secreted into the gland lumina or ir gut wall. Because these secretions dissect through the gut wall, they facilitate exte worsen the prognosis. Cancers of the anal zone are predominantly squamous cell

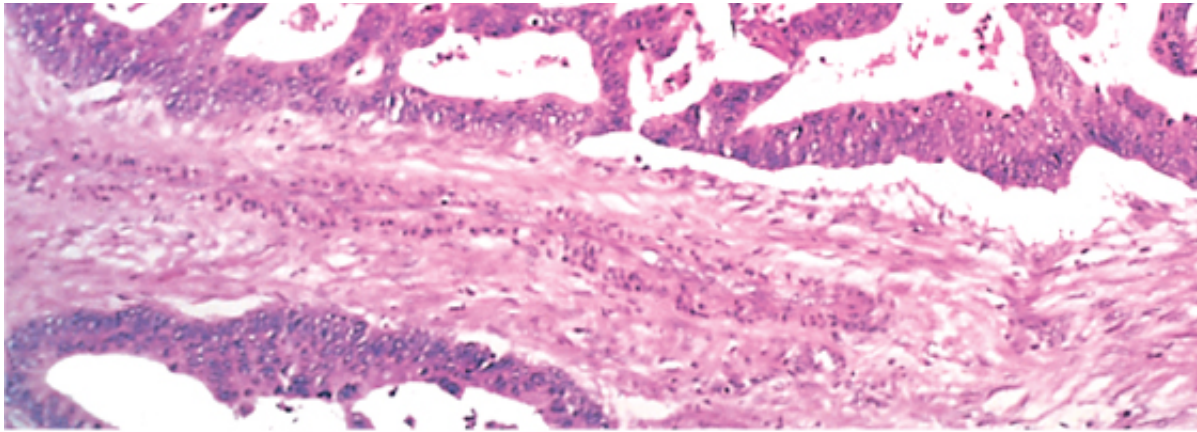






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Figure 15-42 Carcinoma of the descending colon. This circumferential tumor has heaped-up edges and an ulcerated mucosal polyps.





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Figure 15-43 Invasive adenocarcinoma of colon showing malignant glands infiltratin

### Clinical Features

Colorectal cancers remain asymptomatic for years; symptoms develop insidiously and frequently | sometimes years, before diagnosis. Cecal and right colonic cancers most often are called to clinic weakness, and iron deficiency anemia. Left-sided lesions may produce occult bleeding, changes i quadrant discomfort. Although anemia in females may arise from gynecologic causes, it is a clinic *an older man means gastrointestinal cancer until proved otherwise.*

All colorectal tumors spread by direct extension into adjacent structures and by metastasis throug order of preference, the favored sites for metastasis are the regional lymph nodes, liver, lungs, an including the serosal membrane of the peritoneal cavity. In general, the disease spreads beyond t 30% of patients. Carcinomas of the anal region are locally invasive and metastasize to regional ly of malignant tumors of the anal canal are squamous cell carcinomas.

**Table 15-13. TNM Staging of Colon Cancers**

<b>Tumor (T)</b>
T0 = none evident
Tis = in situ (limited to mucosa)
T1 = invasion of lamina propria or submucosa
T2 = invasion of muscularis propria
T3 = invasion through muscularis propria into subserosa or nonperitonealized perimuscular tissue
T4 = invasion of other organs or structures
<b>Lymph Nodes (N)</b>
0 = none evident
1 = 1 to 3 positive pericolic nodes
2 = 4 or more positive pericolic nodes
3 = any positive node along a named blood vessel
<b>Distant Metastases (M)</b>
0 = none evident
1 = any distant metastasis
<b>5-Year Survival Rates</b>
T1 = 97%
T2 = 90%
T3 = 78%
T4 = 63%

Any T; N1; M0 = 66%
Any T; N2; M0 = 37%
Any T; N3; M0 = data not available
Any M1 = 4%

The detection and diagnosis of colorectal neoplasms rely on a variety of methods, beginning with testing for occult blood loss. Barium enema, sigmoidoscopy, and colonoscopy require confirmatory tomography and other radiographic studies are usually used to assess metastatic spread. Serum blood levels of carcinoembryonic antigen, are of little diagnostic value, because they reach significant levels only after the tumor has achieved considerable size and has very probably spread. Moreover, "positive" carcinoembryonic antigen levels are also found in many non-neoplastic conditions, including chronic pancreatitis, and ulcerative colitis. Because *APC* mutations occur early in most colon cancers, microsatellite instability (MSI) testing, which evaluates the length of DNA sequences in epithelial cells, isolated from stools, is being evaluated as a diagnostic test. As mentioned earlier, MSI testing is always performed early in the development of colorectal tumors. Other tests under development involve testing for methylation in DNA isolated from stool cells.

The single most important prognostic indicator of colorectal carcinoma is the extent (stage) of the tumor. The American Joint Commission on Cancer uses the TNM classification ([Table 15-13](#)). The challenge with curative resection is possible, preferably in their "infancy" when they are still adenomatous polyps.

### SUMMARY

**Colorectal Carcinoma** Common tumor in developing countries, with peak incidence in the 5th and 6th decades of life. Almost all are adenocarcinomas, most frequently originating from adenomatous polyps. Two molecular pathways of colorectal carcinogenesis, the adenoma-carcinoma sequence and the microsatellite instability (MSI) pathway. In each pathway there is an accumulation of mutations in specific genes (e.g. *APC* and DNA mismatch repair genes). The tumors are usually exophytic and polypoid masses or annular lesions, composed of malignant cells with varying degrees of differentiation.

## Neoplasms of the Small Intestine

Whereas the small bowel represents 75% of the length of the alimentary tract, its tumors account for only about 1% of all gastrointestinal malignancies. The number of deaths in the United States due to small bowel tumors is about 1% of gastrointestinal malignancies. The most frequent benign tumors in the small intestine are lipomas, followed by various neurogenic, vascular, and hamangiomas. Intestinal adenocarcinomas and carcinoids have a roughly equal incidence. Gastrointestinal stromal tumors (GISTs) have attracted attention recently, because they have an activating mutation affecting *KIT*, a tyrosine kinase receptor (discussed in the next section).

### *Adenocarcinoma of the Small Intestine*

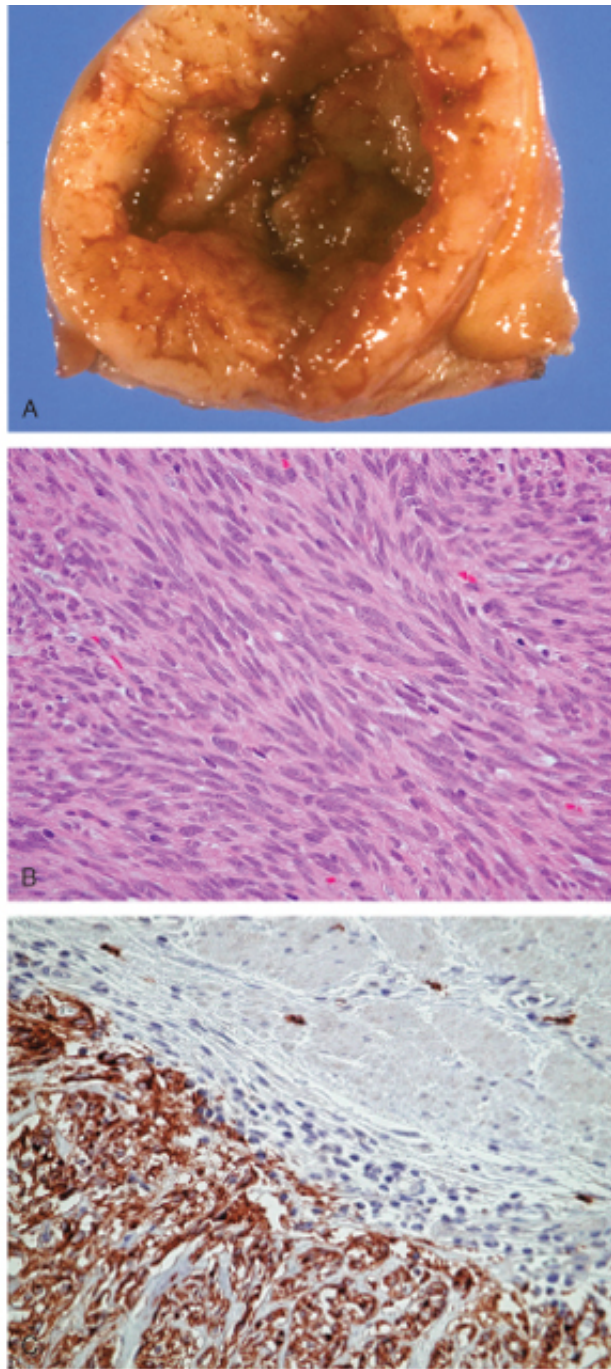
These tumors grow in a napkin-ring encircling pattern or as polypoid fungating masses, in a manner similar to colorectal carcinomas. Adenocarcinomas arise in the duodenum (including the ampulla of Vater). Cramping pain, nausea, and weight loss are common presenting signs and symptoms, but such manifestations generally appear late in the course of the disease. At the time of diagnosis, most have already penetrated the bowel wall, invaded the mesentery or other segment of the small intestine, and sometimes metastasized to the liver and more widely. Despite these problems, wide en bloc resection can result in a survival rate of about 70%. Adenomas of the small intestine may present with anemia or rarely intussusception. Adenocarcinomas of the small intestine in the immediate vicinity of the ampulla of Vater may produce biliary obstruction causing jaundice.

## Other Tumors of the Gastrointestinal Tract

### *Gastrointestinal Stromal Tumors*







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 Figure 15-44 Gastrointestinal stromal tumor (GIST). **A**, GIST from the stomach wall. **B**, Histology of the tumor showing spindle cell composition, chromatin, and eosinophilic fibrillar cytoplasm. **C**, KIT stain showing strong and uniform reactivity of the tumor cells compared to the normal muscle wall. (Courtesy of Dr. Brian Rubin, Department of Pathology, University of Washington)

In the past, these tumors were considered to be smooth muscle tumors, either benign leiomyoma or leiomyosarcoma, sometimes with a spindle cell composition. However, on the basis of a molecular marker common to all gastrointestinal stromal tumors (GISTs), the use of immunohistochemical markers, GISTs are now classified into four types: (a) tumors showing smooth muscle cell differentiation (the most common type); (b) tumors with neural differentiation; (c) tumors with smooth muscle/neural dual differentiation, and (d) tumors with undifferentiated lineage. GISTs constitute the majority of nonepithelial tumors of the stomach but can be present in any part of the gastrointestinal tract.



44). An important advance in understanding the pathogenesis of these tumors, which had an imm treatment, was the recognition that *most GISTs have a somatic mutation in the c-KIT (CD117) gene receptor*. Mutations in this receptor (generally in exon 11) lead to constitutive signaling from the re

There seem to be no differences in the frequency of the mutation among the various histologic typ The preferred sites for metastases of the malignant tumors are the liver, peritoneum, and lungs. In years after removal of the original tumor. The recognition of the molecular defect in GISTs has led specifically targeted to the tumor cells ("targeted therapy"). The tyrosine kinase inhibitor *imatinib* n the treatment of individuals with chronic myeloid leukemia, has been used very successfully in the mutation. Nevertheless, because of the development of resistance to this agent after prolonged tr tyrosine kinase receptor signaling are being tested for clinical use.

### **Gastrointestinal Lymphoma**

Any segment of the gastrointestinal tract may be involved secondarily by systemic dissemination ( to 40% of lymphomas arise in sites other than lymph nodes, and the gut is the most common extr gastrointestinal malignancies are lymphomas. *By definition, primary gastrointestinal lymphomas n bone marrow involvement at the time of diagnosis*; regional lymph node involvement may be pres B- or T-cell origin. The most common form in Western countries is *MALT lymphoma*. This is a spe of the *mucosa-associated lymphoid tissue* (MALT) of the gastrointestinal tract. This type of gastro adults, lacks a sex predilection, and may arise anywhere in the gut: stomach (55% to 60% of case proximal colon (10% to 15%), and distal colon ( $\leq 10\%$ ). The appendix and esophagus are only rari

Gastric MALT lymphomas arise in the setting of mucosal lymphoid activation, as a result of *Helic H. pylori* infection, there is an intense activation of T and B cells in the mucosa. This leads to poly the emergence of a monoclonal B-cell neoplasm. MALT lymphoma cells are CD5 and CD10 nega common (the translocation creates a fusion gene between the apoptosis inhibitor *BCL-2* gene in c chromosome 18).

Primary gastrointestinal lymphomas generally have a better prognosis than do those arising in oth chemotherapy, and radiation therapy offer reasonable hopes of cure. About 50% of gastric lymph treatment for *H. pylori*. Those that do not regress usually contain the t(11;18) translocation or othe (discussed earlier) is associated with a higher than normal risk of intestinal T-cell lymphomas.

### **Carcinoids**

Cells generating bioactive compounds, particularly peptide and nonpeptide hormones, are normal gastrointestinal tract mucosa and have a major role in coordinated gut function. Endocrine cells a the tumors that develop from these cells arise in the gut. Tumors arising from these endocrine cel develop in the pancreas or peripancreatic tissue, lungs, biliary tree, and even liver. The term *carci like*," which has persisted through the decades. The peak incidence of these neoplasms is in the s age. *They compose less than 2% of colorectal malignancies but almost half of small intestinal ma*

Although all carcinoids are potentially malignant tumors, the tendency for aggressive behavior cor local penetration, and the size of the tumor. For example, *appendiceal and rectal carcinoids infreq* may show extensive local spread. By contrast, 90% of ileal, gastric, and colonic carcinoids that ha muscle wall have spread to lymph nodes and distant sites at the time of diagnosis, especially thos

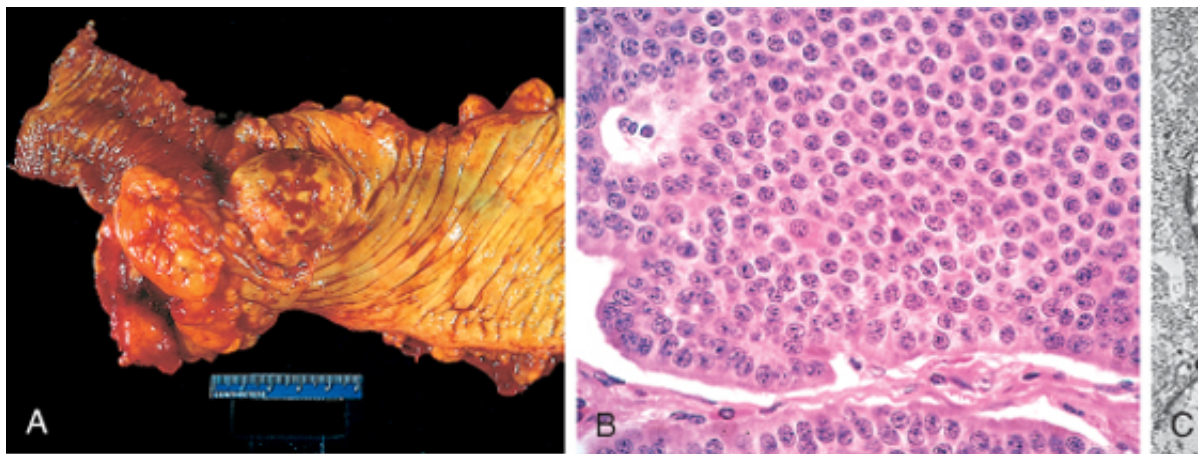
As with normal gut endocrine cells, the cells of carcinoid tumors can synthesize and secrete a var Although multiple hormones may be synthesized by a single tumor, when a tumor secretes a prec syndrome, it may be called by that name (e.g., gastrinoma, somatostatinoma, and insulinoma).

#### **Morphology**

The appendix is the most common site of gut carcinoid tumors, followed by the sm ileum), rectum, stomach, and colon. In the appendix they appear as bulbous swell frequently obliterate the lumen. Elsewhere in the gut, they appear as intramural or create small, polypoid, or plateau-like elevations rarely larger than 3 cm in diamete overlying mucosa may be intact or ulcerated, and the tumors may permeate the bc

mesentery. Those that arise in the stomach and ileum are frequently multicentric, but can be solitary lesions. **A characteristic feature is a solid, yellow-tan appearance** and they are exceedingly firm because of desmoplasia; and when these fibrosing lesions are present in the small bowel they may cause sufficient angulation or kinking to cause obstructive symptoms. Metastases are usually small, dispersed nodules and rarely achieve the size seen in the primary. Notably, **rectal and appendiceal carcinoids almost never metastasize**.

Histologically, the neoplastic cells may form discrete islands, trabeculae, strands, cords, or sheets. Whatever their organization, the tumor cells are monotonously similar, have scant cytoplasm and a round-to-oval stippled nucleus. In most tumors there is minimal mitotic activity, and mitoses are infrequent or absent (Fig. 15-45B). By electron microscopy (Fig. 15-45C) most tumors contain cytoplasmic, membrane-bound secretory granules with osmophilic contents (dense-core granules). Most carcinoids can be shown to contain chromogranin A, synaptophysin, and/or enolase. Specific hormonal peptides may occasionally be identified by immunocytochemistry.



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Figure 15-45 Carcinoid tumor. **A**, Multiple protruding tumors are present at the ileocecal junction. **B**, The tumor cells are arranged in cords and trabeculae with intervening fibrovascular stroma. (H&E). **C**, Electron micrograph showing dense-core secretory granules in the cytoplasm.

### Clinical Features

Gastrointestinal carcinoids are frequently asymptomatic, including virtually all that arise in the appendix. Local symptoms secondary to angulation or obstruction of the small intestine. However, the secretory products can produce a variety of syndromes or endocrinopathies. Gastric, peripancreatic, and pancreatic carcinoids can enter the systemic circulation and can produce the Zollinger-Ellison syndrome by excess elaboration of gastrin, the adrenocorticotrophic hormone secretion, hyperinsulinism, and others. In some instances, these tumors are extremely difficult to find, even during surgical exploration.

Some neoplasms are associated with a distinctive *carcinoid syndrome*, detailed in Table 15-14. The syndrome is present in 10% of patients with carcinoids and in 20% of those with widespread metastases. The precise basis of the syndrome is not clear, but the most common manifestations are thought to arise from elaboration of serotonin (5-hydroxytryptamine [5-HT]) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) are present in the blood and urine of most individuals with the syndrome. Thus, with gastrointestinal carcinoids, hepatic metastases must be present for the development of the syndrome. The possibility that other secretory products, such as prostaglandins, contribute to the manifestations of this syndrome has not been excluded.

The 5-year survival rate for carcinoids (excluding appendiceal) is approximately 90%. Even with metastases to the liver, it is better than 50%. However, widespread disease usually causes death.

**Table 15-14. Clinical Features of the Carcinoid Syndrome**

Vasomotor disturbances
Cutaneous flushes and apparent cyanosis (most patients)
Intestinal hypermotility
Diarrhea, cramps, nausea, vomiting (most patients)
Asthmatic bronchoconstrictive attacks
Cough, wheezing, dyspnea (about one-third of patients)
Hepatomegaly
Nodular, related to hepatic metastases (some cases)
Niacin <sub>Rx</sub> deficiency (due to shunting of niacin <sub>Rx</sub> to serotonin synthesis)
Systemic fibrosis
Cardiac involvement
Pulmonic and tricuspid valve thickening and stenosis
Endocardial fibrosis, principally in right ventricle (bronchial carcinoids affect the left side)
Retroperitoneal and pelvic fibrosis
Collagenous pleural and intimal aortic plaques

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## 16 The Liver, Gallbladder, and Biliary Tract

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### THE LIVER

The liver and its companion biliary tree and gallbladder are considered together because of their anatomic proximity, their interrelated functions, and the overlapping features of some of the diseases that affect these organs. Most of the chapter is about the liver, because it has a far greater role in normal physiology and is the site of a wide variety of diseases.

Residing at the crossroads between the digestive tract and the rest of the body, the liver has the enormous task of maintaining the body's metabolic homeostasis. This includes the processing of dietary [amino acids](#)<sup>®</sup>, carbohydrates, lipids, and vitamins; synthesis of serum proteins; and detoxification and excretion into bile of endogenous waste products and xenobiotics. Thus, it is not surprising that the liver is vulnerable to a wide variety of metabolic, toxic, microbial, and circulatory insults. In some instances, the disease process is primary to the liver. In others the hepatic involvement is secondary, often to some of the most common diseases in humans, such as cardiac decompensation, diabetes, and extrahepatic infections.

The liver has enormous functional reserve, and regeneration occurs in all but the most fulminant of hepatic diseases. Surgical removal of 60% of the liver of a normal person produces minimal and transient hepatic impairment, and regeneration restores most of the liver mass within 4 to 6 weeks. In persons with massive hepatocellular necrosis that has not destroyed the hepatic reticulin framework, almost perfect restoration may occur if the individual can survive the metabolic insult of liver failure. The functional reserve and the regenerative capacity of the liver mask to some extent the clinical impact of early liver damage. However, with progression of diffuse disease or disruption of the circulation or bile flow, the consequences of deranged liver function become life-threatening.

Hepatic disorders have far-reaching consequences, given the crucial dependence of other organs on the metabolic function of the liver. Liver injury and its manifestations tend to follow characteristic morphologic and clinical patterns, regardless of cause. We first summarize the main morphologic patterns that occur in liver injury and then present a general description of the main clinical syndromes of liver disease. The remainder of the chapter describes the principal features of individual hepatic diseases.





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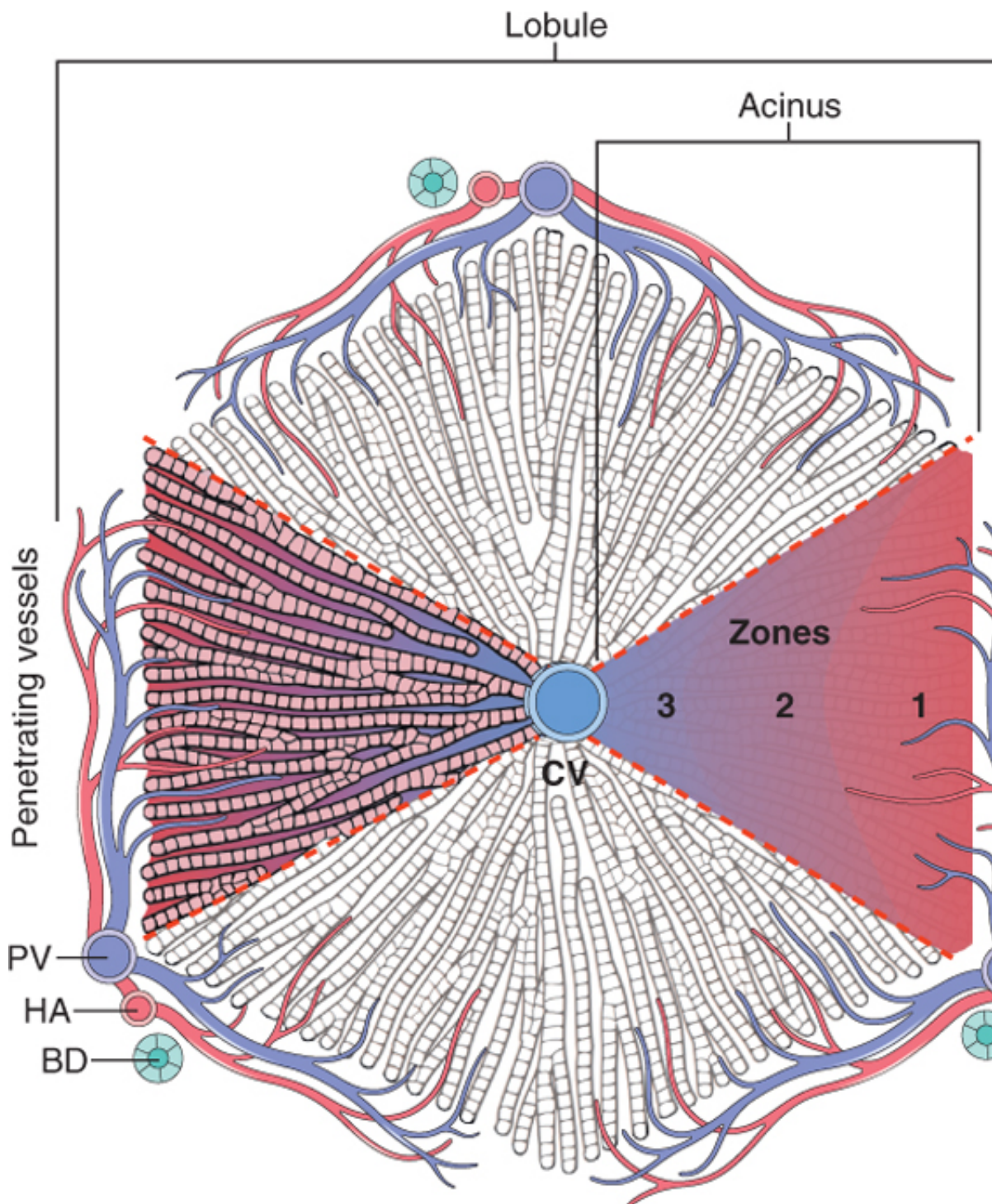
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## PATTERNS OF HEPATIC INJURY



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Figure 16-1 Microscopic architecture of the liver parenchyma. Both a lobule and an acinus are represented. The central vein (CV) is centered around a central vein (CV), also known as terminal hepatic venule, and has portal tracts at three of its apices. The portal tracts contain branches of the portal vein (PV), hepatic artery (HA), and the bile duct (BD).



system. Regions of the lobule are generally referred to as "periportal," "midzonal," and "centrilobular," according to proximity to portal spaces and central vein. Another way of defining the architecture of the liver parenchyma is to use blood supply as a source of reference. Using this approach, triangular acini can be recognized. Acini have at their bases branches of portal vessels that penetrate the parenchyma ("penetrating vessels"). On the basis of the distance from blood supply, the acinus is divided into zones 1 (closest to blood source), 2, and 3 (farthest from blood source).

Here we describe the main patterns of morphologic liver injury and associated cellular responses. Some of these changes are localized to certain regions of the liver lobule (Fig. 16-1).

**Degeneration and intracellular accumulation.** Moderate cell swelling caused by toxic or immunologic insults is reversible. However, more serious damage to hepatocytes may cause marked cell enlargement (*ballooning degeneration*), with irregularly clumped cytoplasm and large, clear spaces. Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material. Accumulation of fat droplets within hepatocytes is known as *steatosis*. Multiple tiny droplets that do not displace the nucleus are known as *microvesicular steatosis* and appear in such conditions as alcoholic liver disease, Reye syndrome, and acute fatty liver of pregnancy. A single large droplet that displaces the nucleus, *macrovesicular steatosis*, may be seen in alcoholic liver disease or in the livers of obese or diabetic individuals. Retained biliary material may impart a diffuse, foamy, swollen appearance to the hepatocyte (known as *feathery degeneration*). **Necrosis and apoptosis.** Virtually any significant insult to liver may cause hepatocyte destruction. In coagulative necrosis, poorly stained mummified hepatocytes remain. In apoptosis, isolated hepatocytes become shrunken, pyknotic, and intensely eosinophilic (these patterns are described in Chapter 1). In the setting of ischemia, several drug and toxic reactions, hepatocyte necrosis is distributed immediately around the central vein (*centrilobular necrosis*), extending into the midzonal area. Pure midzonal and periportal necrosis is rare. In most types of hepatic injury, a variable mixture of inflammatory hepatocyte death is encountered. Cell death may be limited to scattered cells within the hepatic parenchyma or to the interface between the periportal parenchyma and inflamed portal tract (*interface hepatitis*). With more severe inflammatory or toxic injury, apoptosis or necrosis of contiguous hepatocytes may span adjacent lobules in a portal-to-portal, portal-to-central, or central-to-central fashion (*bridging necrosis*). Destruction of entire lobules (*submassive necrosis*) or most of the liver parenchyma (*massive necrosis*) is usually accompanied by hepatic failure. **Regeneration.** Cell death or tissue resection (such as in living-donor transplantation) triggers hepatocyte replication, to compensate for the cell or tissue loss. Hepatocyte proliferation is recognized by the presence of mitoses or by the detection of cell cycle markers by immunocytochemical staining. The cells of the canals of Hering constitute a reserve compartment of progenitor cells for hepatocytes and bile duct cells. Cells of this reserve compartment, known as *oval cells*, proliferate when hepatocytes are unable to replicate or exhausted their replicative capacity. **Inflammation.** Injury to hepatocytes associated with an influx of acute or chronic inflammatory cells into the liver is termed *hepatitis*. Although hepatocyte necrosis may precede the onset of inflammation, the converse is also true. Lysis of antigen-expressing liver cells by sensitized T cells is the cause of liver damage in some forms of viral hepatitis. Inflammation may be limited to portal tracts or may spill over into the parenchyma. Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction. **Fibrosis.** Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver. Deposition of collagen has lasting consequences on hepatic patterns of blood flow and perfusion of hepatocytes. In the initial stages, fibrosis may develop within or around portal tracts (*portal or periportal fibrosis*) or around the central vein, or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes (*pericellular fibrosis*). With time, fibrous strands link regions of the liver (portal-to-portal, portal-to-central, central-to-central), a process called *bridging fibrosis*. **Cirrhosis.** With progressive parenchymal injury and fibrosis, the liver develops nodules of regenerating hepatocytes surrounded by bands of scar tissue. In this process, the normal liver architecture is destroyed, and the condition is termed cirrhosis. Depending on the size of the nodules (smaller or larger than 3 mm), cirrhosis can be classified as being micronodular or macronodular. However, this classification has little relevance for

as being micronodular or macronodular. However, this classification has little relevance for pathogenesis or clinical course of the disease. Cirrhosis is an end-stage liver disease, and also increases the risk of malignancy. *Ductular reaction*. In biliary and other forms of liver disease, the number of intrahepatic bile ducts and canals of Hering may increase. This change is known as a ductular reaction. The proliferation of biliary ductules is usually associated with fibrosis and inflammation. Ductular reaction has gained much interest recently, because some of the proliferating cells originating from the canals of Hering can function as progenitor cells for hepatocytes and bile ducts.



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## CLINICAL SYNDROMES

The ebb and flow of hepatic injury may be imperceptible to the individual, or hepatic function may. The major clinical syndromes of liver disease are hepatic failure, cirrhosis, portal hypertension, and characteristic clinical manifestations ([Table 16-1](#)), and a battery of laboratory tests are used to diagnose these conditions. These conditions are discussed next.

### Hepatic Failure

**Table 16-1. Clinical Consequences of Liver Disease**

Characteristic Signs of Severe Hepatic Dysfunction
Jaundice and cholestasis
Hypoalbuminemia
Hyperammonemia
Hypoglycemia
Palmar erythema
Spider angiomas
Hypogonadism
Gynecomastia
Weight loss
Muscle wasting
Portal Hypertension Associated with Cirrhosis
Ascites
Splenomegaly
Esophageal varices
Hemorrhoids
Caput medusae-abdominal skin
Complications of Hepatic Failure
Coagulopathy
Hepatic encephalopathy
Hepatorenal syndrome

**Table 16-2. Laboratory Evaluation of Liver Disease**

Test Category	Serum Measurement*
Hepatocyte integrity	Cytosolic hepatocellular enzymes†
	<i>Serum aspartate aminotransferase (AST)</i>
	<i>Serum alanine aminotransferase (ALT)</i>
	Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances secreted in bile†
	<i>Serum bilirubin</i>
	<i>Total:</i> unconjugated plus conjugated
	<i>Direct:</i> conjugated only
	<i>Delta:</i> covalently linked to albumin
	Urine bilirubin
	Serum bile acids

	Serum bile acids
	Plasma membrane enzymes† (from damage to bile canaliculus)
	<i>Serum alkaline phosphatase</i>
	Serum $\gamma$ -glutamyl transpeptidase
	Serum 5'-nucleotidase
Hepatocyte function	Proteins secreted into the blood
	<i>Serum albumin</i> ‡
	<i>Prothrombin time</i> † (factors V, VII, X, prothrombin, fibrinogen)
	Hepatocyte metabolism Serum ammonia†
	Aminopyrine breath test (hepatic demethylation)
	Galactose elimination (intravenous injection)

\*Most common tests are in italics.

†An elevation implicates liver disease.

‡A decrease implicates liver disease.

The most severe clinical consequence of liver disease is hepatic failure. It generally develops as the liver, either by insidious destruction of hepatocytes or by repetitive discrete waves of parenchymal failure is the result of sudden and massive destruction of hepatic tissue. Whatever the sequence, liver failure is lost before hepatic failure ensues. In many cases, the balance is tipped toward decompensation by increased demands on the liver. These include systemic infections, electrolyte disturbances, stress (major surgery), and bleeding.

The alterations that cause liver failure fall into three categories:

1. *Acute liver failure with massive hepatic necrosis*. This is most often caused by *drugs* or *fulminant hepatitis*. It denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within a course extending as long as 3 months is called subacute failure. *The histologic correlate of acute liver failure is massive necrosis*. It is an uncommon but life-threatening condition that often requires liver transplantation. It is discussed later in this chapter.
2. *Chronic liver disease*. This is the most common route to hepatic failure and is the end point of many chronic liver diseases ending in cirrhosis. The many causes of cirrhosis are discussed later.
3. *Hepatic dysfunction without overt necrosis*. Hepatocytes may be viable but unable to perform their normal functions. Examples include fatty liver of pregnancy (which can lead to acute liver failure a few days after onset), tetracycline-induced fatty liver and encephalopathy in children, associated with *aspirin* intake and

### Clinical Features

Regardless of cause, the clinical signs of hepatic failure occurring in individuals with chronic liver disease are an almost invariable finding. Impaired hepatic synthesis and secretion of albumin leads to *hypoproteinaemia* and peripheral edema. *Hyperammonemia* is attributable to defective hepatic *urea* cycle function. On the other hand, impaired metabolism and consequent hyperestrogenemia are the putative causes of *palmar erythema* (a redness of the palms) and *angiomas* of the skin. Each angioma is a central, pulsating, dilated arteriole from which small vessels radiate. Hyperestrogenemia also leads to *hypogonadism* and *gynecomastia*. Acute liver failure may present with signs that are notably absent on physical examination are stigmata of chronic liver disease (e.g., gynecomastia,

Hepatic failure is life-threatening for several reasons. The accumulation of toxic metabolites may lead to multi-organ failure. In impaired liver function, patients are highly susceptible to failure of multiple organ systems. Thus, if sepsis combines with renal failure to claim the lives of many individuals with hepatic failure. A coagulopathy due to impaired hepatic synthesis of blood clotting factors. The resultant bleeding tendency may lead to bleeding in the gastrointestinal tract as well as bleeding elsewhere. Intestinal absorption of blood places a metabolic load on the liver that may exacerbate the failure. The outlook of full-blown hepatic failure is particularly grave for persons with chronic liver disease. Death occurring within weeks to a few months in about 80% of cases. About 40% of individuals with liver failure die spontaneously. The others either die without transplantation (~30%) or receive a liver transplant.



Two particular complications merit separate consideration, because they herald the most grave stages of liver disease: hepatic encephalopathy and hepatorenal syndrome.

### ***Hepatic Encephalopathy***

Hepatic encephalopathy is a feared complication of acute and chronic liver failure. Patients show a wide range of mental and motor function, ranging from subtle behavioral abnormalities to marked confusion and stupor, to deep coma. The disorder can progress over hours or days as, for example, in fulminant hepatic failure or, more insidiously, in some cases of chronic liver disease. Associated fluctuating neurologic signs include rigidity, hyper-reflexia, and abnormal reflexes, and, rarely, seizures. Particularly characteristic is *asterixis* (also called flapping tremor), consisting of extension-flexion movements of the head and extremities, best seen when the arms are held in extension.

In most instances there are only minor morphologic changes in the brain, such as edema and an increase in the number of glial cells. Two conditions seem to be important in the genesis of this disorder: (1) severe loss of hepatocellular function, leading to a shunting of portal to systemic circulation around the chronically diseased liver. The net result is exposure of the brain to the acute setting, an elevation in blood ammonia, which impairs neuronal function and promotes cerebral edema. In the chronic setting, deranged neurotransmission arises from alterations in amino acid metabolism.

### ***Hepatorenal Syndrome***

The hepatorenal syndrome, which appears in individuals with severe liver disease, consists of the primary abnormalities of the kidneys themselves. Excluded by this definition are concomitant damage to the kidneys that may occur with exposure to carbon tetrachloride and certain mycotoxins, and the copper toxicity of Wilson's disease. In advanced hepatic failure in which circulatory collapse leads to acute tubular necrosis and renal function improves if hepatic failure is reversed. Although the exact cause is unknown, evidence points to splanchnic vasoconstriction, leading to severe reduction of renal blood flow, particularly to the cortex. Onset is usually abrupt, with a drop in urine output, associated with rising blood urea nitrogen and creatinine values. *The ability to produce a hyperosmolar urine devoid of proteins and abnormal sediment that is surprisingly low* is a characteristic feature. The renal failure may hasten death in the patient with acute fulminant or advanced chronic hepatic failure. Renal insufficiency (serum creatinine of 2-3 mg/dL) may persist for weeks to months, as in cirrhotic patients receiving dialysis.

### ***Cirrhosis***

Cirrhosis is among the top 10 causes of death in the Western world. Its major causes include alcohol, chronic viral hepatitis, autoimmune hepatitis, biliary disease, and iron overload. Cirrhosis is defined as a *diffuse process of conversion of normal liver architecture into structurally abnormal nodules*. Its three main characteristics are:

*Bridging fibrous septa* in the form of delicate bands or broad scars around multiple adjacent nodules. The process is generally irreversible, although regression has been reported to occur in selected instances. The nodules are very small (<3 mm in diameter, micronodules) to large (several centimeters in diameter, macronodules), separated by fibrotic bands. The nodules generally contain proliferating hepatocytes, although regenerative nodules are not necessary for diagnosis of cirrhosis. *Disruption of the architecture of the entire liver*. The parenchymal cell loss is diffuse throughout the liver; focal injury with scarring does not constitute cirrhosis.

There is no satisfactory classification of cirrhosis save for specification of the presumed underlying cause. The most common causes of cirrhosis are chronic alcoholism and chronic hepatitis B and C, followed by biliary diseases and hemochromatosis. If all these causes have been excluded, about 10% of cases remain, referred to as cryptogenic cirrhosis. The "wastebasket" speaks to the difficulty in establishing an etiologic diagnosis once cirrhosis is well established.

### ***Pathogenesis***

The major mechanisms that combine to create cirrhosis are hepatocellular death, regeneration, and fibrosis. The many causes of hepatocellular destruction are discussed elsewhere in this chapter and include alcohol, viral hepatitis, and autoimmune disease. Development of cirrhosis requires that cell death occur over long periods of time and be accompanied by incomplete regeneration. Regeneration is a normal compensatory response to cell death. Fibrosis is a wound-healing reaction to injury that involves not only the parenchyma but also the supporting connective tissue. In the normal liver, the injury involves not only the parenchyma but also the supporting connective tissue. In the normal liver, the injury involves not only the parenchyma but also the supporting connective tissue.

the injury involves not only the parenchyma but also the supporting connective tissue. In the normal liver, the perisinusoidal space (space of Disse) contains a delicate framework of collagen (fibril-forming collagens types I, III, V, and XI) is present only in the space of Disse. The liver has no true basement membrane; instead, a delicate framework of collagen and other ECM components are deposited in the space of Disse (Fig. 16-2). In advanced liver disease, separate nodules of hepatocytes throughout the liver. Vascular changes consisting of the loss of fenestrations and the development of portal vein-hepatic vein and hepatic artery-portal vein vascular shunts complicate the normal architecture. Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of materials from the blood to hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange. In portal hypertension, the exchange of albumin, clotting factors, lipoproteins) between hepatocytes and the plasma is markedly impaired. This process is aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity.

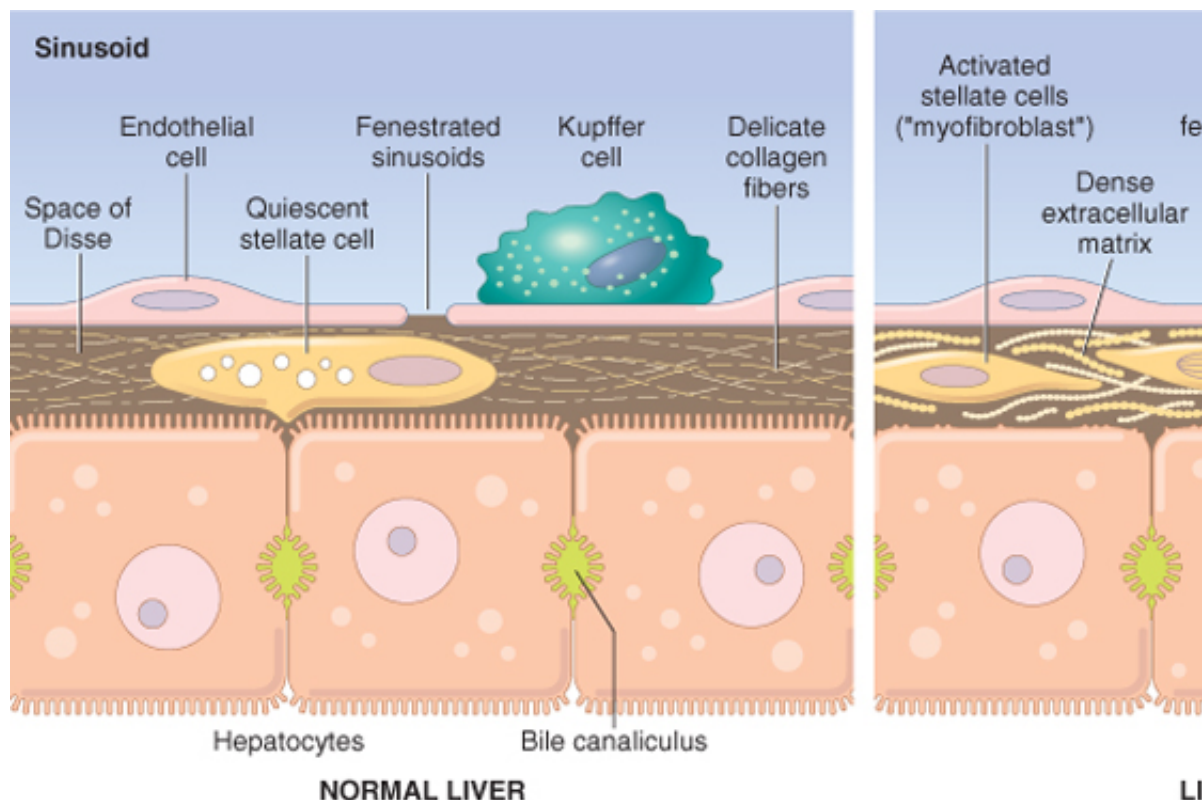


Figure 16-2 Liver fibrosis. In the normal liver, the perisinusoidal space (space of Disse) contains a delicate framework of collagen and other ECM components. In liver fibrosis, stellate cells are activated to produce a dense layer of matrix material that is deposited in the perisinusoidal space, narrowing the sinusoid and preventing the free exchange of materials from the blood. Kupffer cells are also activated and contribute to the fibrosis. Note that this illustration is not to scale; the space of Disse is actually much narrower than shown.

The major source of excess collagen in cirrhosis are the perisinusoidal stellate cells (formerly known as Ito cells) that lie in the space of Disse. Although they normally function as storage cells for vitamin A and fat, they become activated, and transform into myofibroblast-like cells, which express smooth muscle  $\alpha$ -actin. Stimuli for the activation of stellate cells and production of collagen are believed to include reactive oxygen species and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and lymphokines, which are released by hepatocytes or by stimulated Kupffer cells and sinusoidal endothelial cells. Activated stellate cells produce chemokines that cause their further proliferation and collagen synthesis. Transforming growth factor  $\beta$  (TGF- $\beta$ ) is a potent activator of stellate cells. At least in its initial stages, fibrosis is a dynamic process that involves the synthesis and activation of metalloproteinases and also of tissue inhibitors of metalloproteinases.

### Clinical Features

All forms of liver disease can lead to cirrhosis. The most common cause of cirrhosis is chronic hepatitis C, followed by chronic hepatitis B. Alcohol consumption is another major cause of cirrhosis. The clinical features of cirrhosis are discussed in the next section.

All forms of cirrhosis may be clinically silent. When symptomatic they lead to nonspecific manifestations and, in advanced disease, frank debilitation. Progression or improvement in cirrhosis depends on the disease responsible for the cirrhosis. Incipient or overt hepatic failure may develop, usually precipitated on the liver, as from systemic infection or a gastrointestinal hemorrhage. The ultimate mechanism is (1) progressive liver failure, (2) a complication related to portal hypertension, or (3) the development of hepatocellular carcinoma.

## SUMMARY

### Cirrhosis

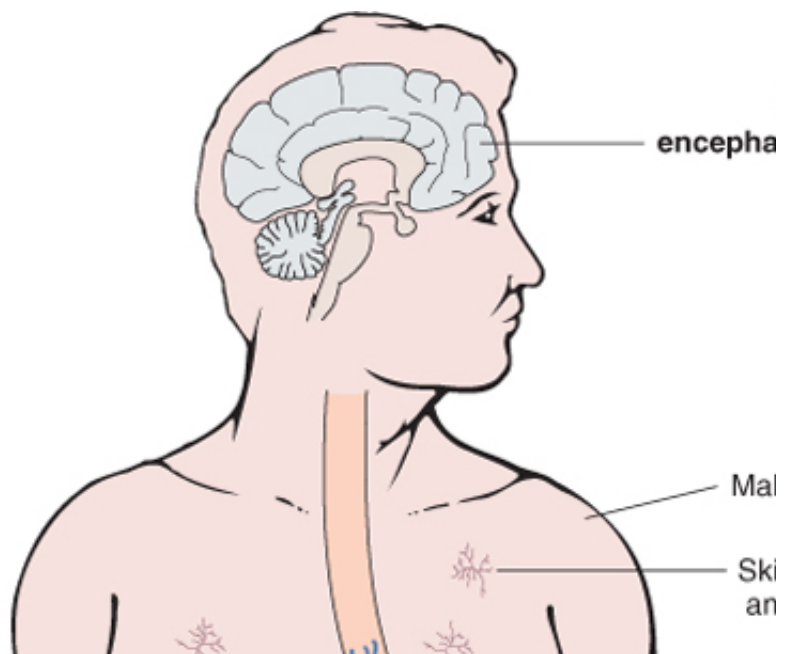
The three main characteristics of cirrhosis are (1) bridging fibrous septa, (2) regenerative nodules containing replicating hepatocytes, and (3) disruption of the architecture of the liver. It is an end-stage liver disease that may have multiple causes. The most frequent are chronic viral hepatitis and chronic alcoholism. Less frequent causes are autoimmune and biliary diseases and conditions such as hemochromatosis. The morphologic features of advanced cirrhosis are similar regardless of the cause of the disease. Nonalcoholic fatty liver disease is a common cause of cirrhosis. The main complications of cirrhosis are related to decreased liver function, portal hypertension, and increased risk of hepatocellular carcinoma.

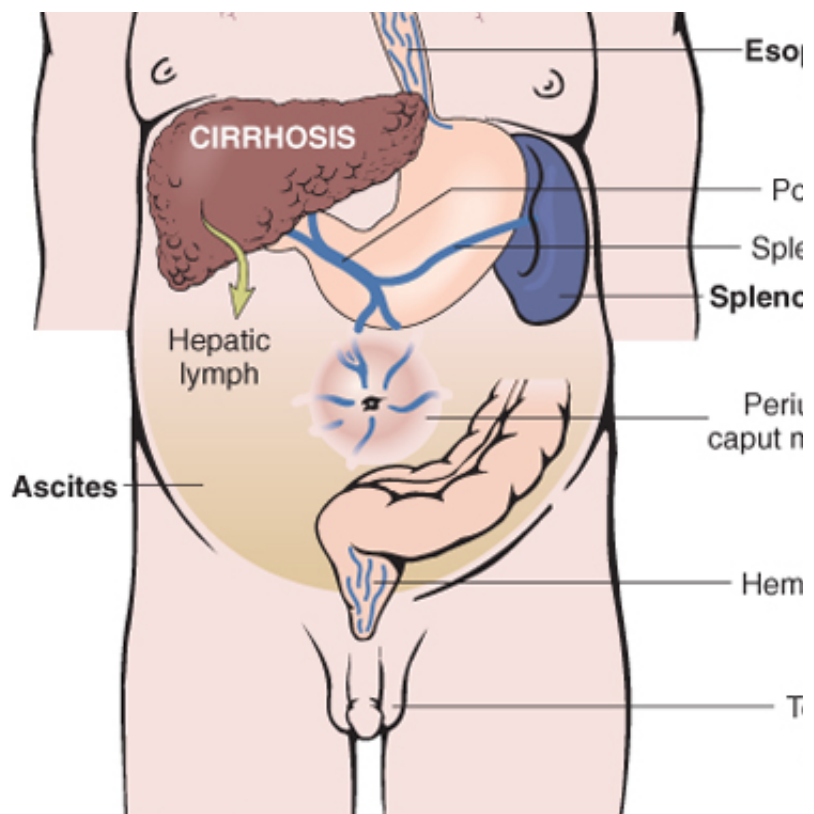
### Portal Hypertension

Increased resistance to portal blood flow may develop from prehepatic, intrahepatic, and posthepatic causes. The *dominant intrahepatic cause is cirrhosis, accounting for most cases of portal hypertension*. Far less frequent causes are fatty change, diffuse granulomatous diseases such as sarcoidosis and miliary tuberculosis, and diseases of the microcirculation, exemplified by nodular regenerative hyperplasia (discussed later).

Portal hypertension in cirrhosis results from increased resistance to portal flow at the level of the portal vein and its branches by perivenular fibrosis and expanded parenchymal nodules. Anastomoses between the portal and systemic veins also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal system. The major clinical consequences are (1) ascites, (2) the formation of portosystemic venous shunts, (3) hepatic encephalopathy (discussed earlier). The manifestations of portal hypertension in the setting of cirrhosis are (1) ascites, (2) portosystemic shunts, and (3) hepatic encephalopathy.

### Ascites





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Figure 16-3 Some clinical consequences of portal hypertension in the setting of cirrhosis. The most important n

Ascites refers to the collection of excess fluid in the peritoneal cavity. It usually becomes clinically accumulated, but many liters may collect and cause massive abdominal distention. It is generally of protein (largely albumin) as well as the same concentrations of solutes such as [glucose<sup>®</sup>](#), sodium. The fluid may contain a scant number of mesothelial cells and mononuclear leukocytes. Influx of neutrophils whereas red cells point to possible disseminated intra-abdominal cancer. With long-standing ascites transdiaphragmatic lymphatics may produce hydrothorax, more often on the right side.

The pathogenesis of ascites is complex, involving one or more of the following mechanisms:

*Sinusoidal hypertension*, alters Starling forces and drives fluid into the space of Disse, which this movement of fluid is also promoted by hypoalbuminemia. *Leakage of hepatic lymph* into the peritoneal cavity. Normal lymph flow approximates 800 to 1000 mL/day. With cirrhosis, hepatic lymphatic flow exceeds thoracic duct capacity. Hepatic lymph is rich in proteins and low in triglycerides, as reflecting *retention of sodium and water* due to secondary hyperaldosteronism ([Chapter 4](#)), despite a normal.

### **Portosystemic Shunt**

With the rise in portal venous pressure, bypasses develop wherever the systemic and portal circulations are veins around and within the rectum (manifest as hemorrhoids), the cardioesophageal junction (varices), the retroperitoneum, and the falciform ligament of the liver (involving periumbilical and abdominal wall collaterals). Hemorrhoidal bleeding may occur, it is rarely massive or life threatening. Much more important are the dilated subcutaneous veins extending outward from the umbilicus (caput medusae). Abdominal wall collaterals appear as dilated subcutaneous veins extending outward from the umbilicus. This is an important clinical hallmark of portal hypertension.

### **Splenomegaly**



Long-standing congestion may cause congestive splenomegaly. The degree of enlargement varies necessarily correlated with other features of portal hypertension. Massive splenomegaly may select abnormalities attributable to hypersplenism (Chapter 12).

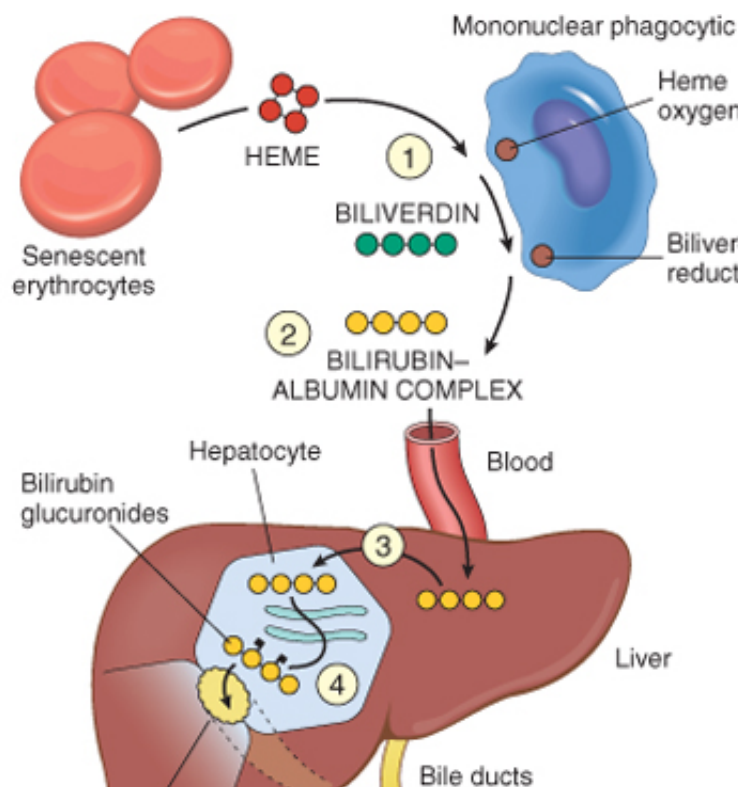
## Jaundice and Cholestasis

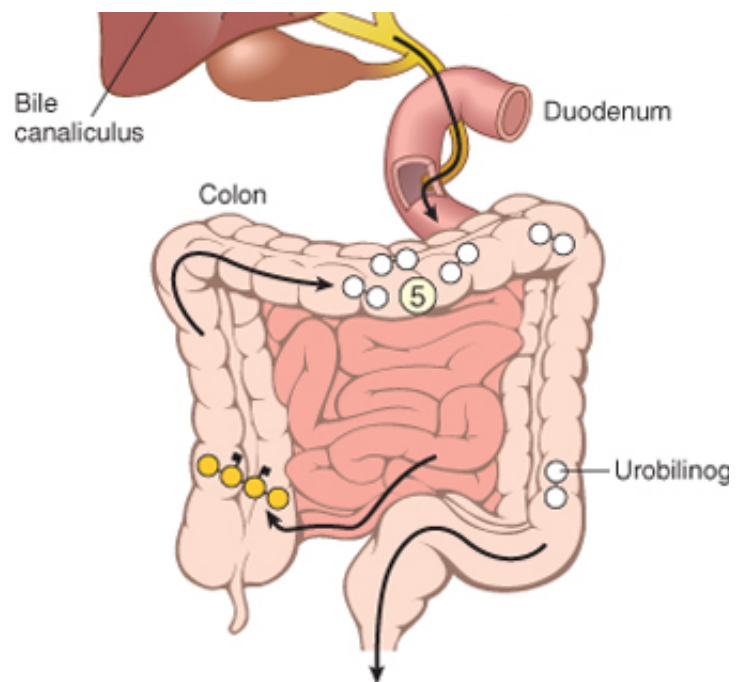
Jaundice, a common manifestation of liver disease, results from the retention of bile. Hepatic bile constitutes the primary pathway for the elimination of bilirubin, excess cholesterol, and xenobiotics excreted into urine. Second, secreted bile salts and phospholipid molecules promote emulsification. Because bile formation is one of the most sophisticated functions of the liver, it is also one of the most vulnerable. The yellow discoloration of skin and sclerae (*icterus*), occurs when systemic retention of bilirubin leads to a level of  $>2$  mg/dL (the normal in the adult is  $<1.2$  mg/dL). *Cholestasis* is defined as systemic retention of not only bile but also of substances eliminated in bile (particularly bile salts and cholesterol).

### Bilirubin and Bile Acids

Bilirubin is the end product of heme degradation (Fig. 16-4). Most of the daily production (0.2-0.3 g) is derived from the breakdown of senescent erythrocytes, with the remainder derived primarily from the turnover of hepatic hemopigments and newly formed erythrocytes in the bone marrow. The latter pathway is important in hematologic disorders such as intramedullary hemolysis of defective erythrocytes (ineffective erythropoiesis; Chapter 12). Whatever the source, heme is converted to biliverdin, which is then reduced to bilirubin by biliverdin reductase. Bilirubin is then taken up by the mononuclear phagocyte system (including the spleen) and bound to serum albumin. Its elimination involves (1) carrier-mediated uptake at the sinusoidal membrane, (2) cytosolic protein binding and (3) conjugation with one or two molecules of glucuronic acid by bilirubin uridine diphosphate-glucuronyl transferase. This process converts the water-soluble, nontoxic bilirubin glucuronides into bile. Most bilirubin glucuronides are deconjugated and degraded to colorless urobilinogens. The urobilinogens and the residue of intact pigment are excreted in the feces. About 20% of the urobilinogens are reabsorbed in the ileum and colon, returned to the liver, and promptly resecreted into the bile. Unconjugated bile acids are also reabsorbed in the ileum and returned to the liver by *enterohepatic* circulation.

### Pathogenesis and Clinical Features





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Figure 16-4 Bilirubin metabolism and elimination. 1, Normal bilirubin production (0.2-0.3 gm/day) is derived primarily from erythrocytes, with a minor contribution from degradation of tissue heme-containing proteins. 2, Extrahepatic bilirubin production. 3, Hepatocellular uptake, and 4, glucuronidation by glucuronosyltransferase in the hepatocytes generates conjugated bilirubin, which is water soluble and readily excreted into bile. 5, Gut bacteria deconjugate the bilirubin and degrade it to urobilinogen, which is water soluble and readily excreted into bile. 6, Residue of intact pigments are excreted in the feces, with some reabsorption and re-excretion.

In the normal adult the rate of systemic bilirubin production is equal to the rates of hepatic uptake, and excretion. Jaundice occurs (bilirubin levels may reach 30-40 mg/dL in severe disease) when the equilibrium is disturbed by one or more of the following mechanisms (Table 16-3): (1) excessive production, (2) decreased hepatic uptake, (3) impaired conjugation, (4) decreased hepatocellular excretion, and (5) impaired bile flow. The first three mechanisms produce unconjugated hyperbilirubinemia, and the latter two produce conjugated hyperbilirubinemia. More than one mechanism may operate to produce jaundice, especially in hepatic failure. In general, however, one mechanism predominates, so that knowledge of plasma bilirubin is of value in evaluating possible causes of hyperbilirubinemia.

**Table 16-3. Main Causes of Jaundice**

<b>Predominantly Unconjugated Hyperbilirubinemia</b>
Excess production of bilirubin
Hemolytic anemias
Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas)
Ineffective erythropoiesis syndromes (e.g., pernicious anemia, thalassemia)
Reduced hepatic uptake
Drug interference with membrane carrier systems
Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
Impaired bilirubin conjugation
Physiologic jaundice of the newborn
<b>Predominantly Conjugated Hyperbilirubinemia</b>
Decreased hepatocellular excretion
Deficiency in canalicular membrane transporters

Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cycloporine)
Hepatocellular damage or toxicity (e.g., viral or drug-induced hepatitis, total parenteral nutrition, systemic
Impaired intra- or extra-hepatic bile flow
Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing chola transplantation)

Of the various causes of jaundice listed in [Table 16-3](#), the most common are hepatitis, obstruction chapter), and hemolytic anemia ([Chapter 12](#)). Because the hepatic machinery for conjugating and until about 2 weeks of age, almost every newborn develops transient and mild unconjugated hype or physiologic jaundice of the newborn.

Jaundice may also result from inborn errors of metabolisms, including:

*Gilbert syndrome* is a relatively common, benign, somewhat heterogeneous inherited cond unconjugated hyperbilirubinemia. The primary cause is decreased hepatic levels of glucurc attributed to a mutation of the responsible gene, additional polymorphisms may play a role disorder. Affecting up to 7% of the population, the hyperbilirubinemia may go undiscovered morbidity. *Dubin-Johnson syndrome* results from an autosomal recessive defect in the trans hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. These hyperbilirubinemia. Other than having a darkly pigmented liver (from polymerized [epinephr](#) hepatomegaly, patients are otherwise without functional problems.

Cholestasis, which results from impaired bile flow due to hepatocellular dysfunction or intrahepatic also present as jaundice. However, sometimes *pruritus* is the presenting symptom, presumably re and their deposition in peripheral tissues, particularly skin. *Skin xanthomas* (focal accumulations c result of hyperlipidemia and impaired excretion of cholesterol. A *characteristic laboratory finding is* an enzyme present in bile duct epithelium and in the canalicular membrane of hepatocytes. An isc tissues such as bone, and so the increased levels must be verified as being hepatic in origin. Oth relate to intestinal malabsorption, including inadequate absorption of the fat-soluble vitamins A, D

Extrahepatic biliary obstruction is frequently amenable to surgical alleviation. By contrast, cholest intrahepatic biliary tree or hepatocellular secretory failure (collectively termed *intrahepatic cholest* (short of transplantation), and the patient's condition may be worsened by an operative procedure a correct diagnosis of the cause of jaundice and cholestasis.

## SUMMARY

### Jaundice and Cholestasis

Jaundice occurs when retention of bilirubin leads to serum levels above 2.0 or extra-hepatic obstruction of bile flow are the most common causes of jau accumulation of conjugated bilirubin. Hemolytic anemias are the most comm involving the accumulation of unconjugated bilirubin. Cholestasis is the impa resulting in the retention of bilirubin, bile acids, and cholesterol. Serum alkali elevated in cholestatic conditions.





## INFECTIOUS AND INFLAMMATORY DISORDERS

Chronic inflammatory disorders of the liver dominate the clinical practice of hepatology. Virtually all chronic liver diseases recruit inflammatory cells. *However, the foremost primary liver infection is viral hepatitis*, which is a condition called *autoimmune hepatitis*, which we will discuss later. The liver is almost always involved systemically or arising within the abdomen. Those in which the hepatic lesion may be prominent include salmonellosis, candidiasis, and amebiasis, which are discussed in the relevant chapters through abscesses will be discussed in this section, and they are presented last.

Systemic viral infections that can involve the liver include (1) infectious mononucleosis (Epstein-Barr virus hepatitis during the acute phase); (2) cytomegalovirus or herpesvirus infections, particularly in the setting of the yellow fever, which has been a major and serious cause of hepatitis in tropical countries. Infrequently, if immunosuppressed, the liver is affected in the course of rubella, adenovirus, or enterovirus infection. *Specified, the term viral hepatitis is reserved for infection of the liver caused by a small group of viruses.* Because these viruses may cause similar patterns of disease, the histologic changes and clinical features are described together, after a presentation of the specific forms of viral hepatitis.

### Viral Hepatitis

The etiologic agents of viral hepatitis (as defined above) are hepatitis viruses A (HAV), B (HBV), C (HCV), and D (HDV). The G virus (HGV) is not pathogenic and will not be considered. [Table 16-4](#) summarizes some of the features of these viruses.

#### Hepatitis A Virus (HAV)

Table 16-4. The Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D
Type of virus Viral family	ssRNA Hepadnavirus; related to picornavirus	partially dsDNA Hepadnavirus	ssRNA Flaviridae	Circular defective ssRNA Subviral particle in C family
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral
Mean incubation period	2-4 weeks	1-4 months	7-8 weeks	Same as HBV
Frequency of chronic liver disease	Never	10%	~80%	5% (coinfection); ≤7% superinfection
Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg	PCR for HCV RNA; 3rd- generation ELISA for antibody detection	Detection of IgM and antibodies; HDV RNA HDAg in liver

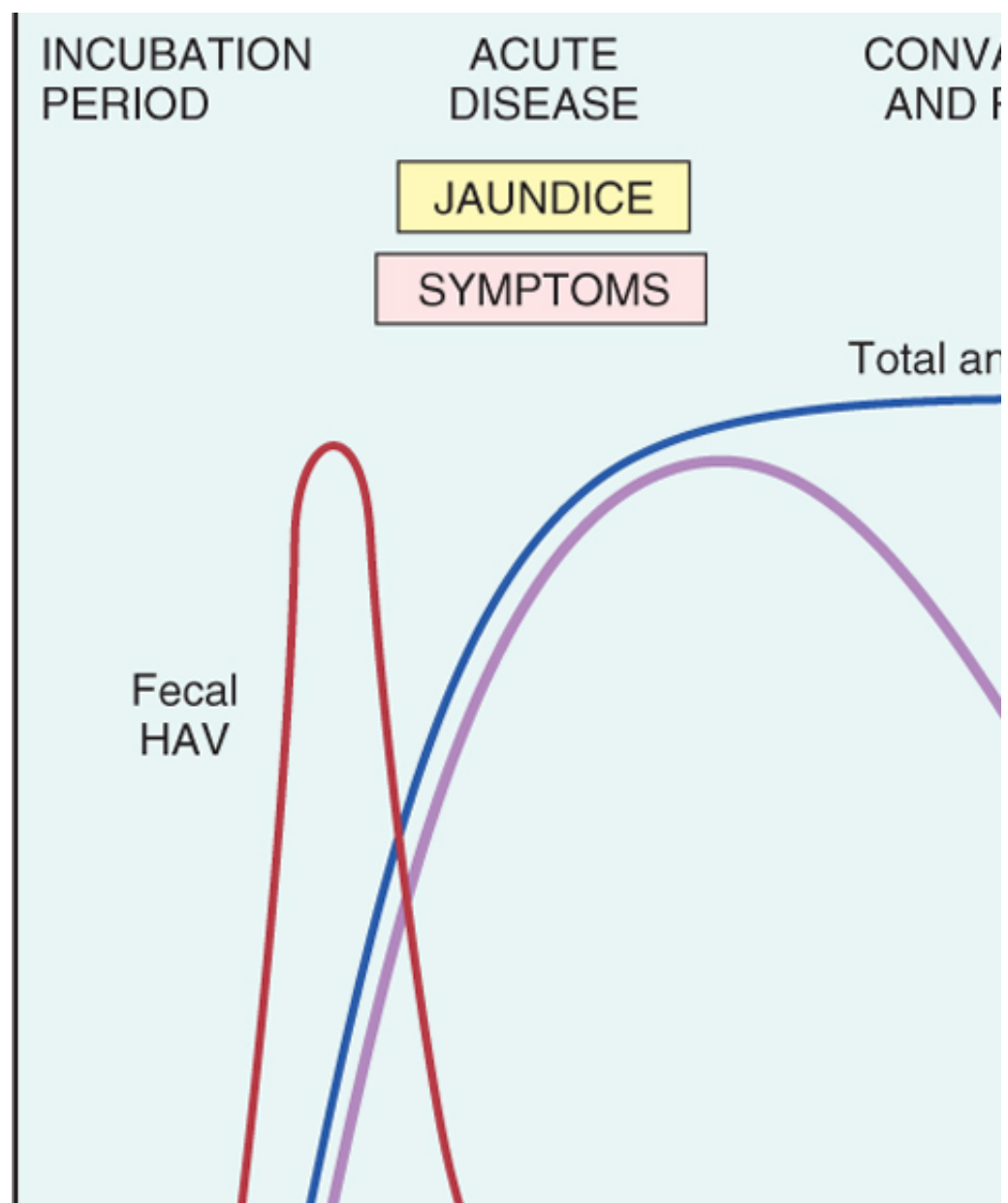
dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; HEV, hepatitis E virus; IV, intravenous; PCR, polymerase chain reaction; P, perinatal; R, rare; S, common; T, transient; W, weeks; Y, years.  
From Washington K: Inflammatory and infectious diseases of the liver. In Iacobuzio-Donahue CA, Montgomery EA (eds): Gastrointestinal Pathology, 2nd ed. Philadelphia, Elsevier, 2005.

Hepatitis A (known for many years as "infectious hepatitis") is a *benign, self-limited disease* with a mean incubation period of (average 28 days). It is an "old" disease, having been described as a contagious jaundice in antiquity (drinking of donkey urine, according to the Babylonian Talmud), and was a major problem for the military in the past. *It does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis. Case fatalities are rare, about 0.1%, and seem to be more likely to occur when patients have preexisting liver disease from other causes.*



Nevertheless, HAV has the largest potential among the hepatitis viruses to cause epidemics. HAV is endemic in countries with poor hygiene and sanitation, so that most natives of such countries have reached the age of 10 years. Clinical disease tends to be mild or asymptomatic (in children) and rare after childhood. In adults, the infection may create considerably greater morbidity than the innocuous childhood infection.

HAV is spread by ingestion of contaminated water and foods and is shed in the stool for 2 to 3 weeks after the onset of jaundice. HAV is not shed in any significant quantities in saliva, urine, or semen. Close personal contact during the period of fecal shedding, with fecal-oral contamination, accounts for most cases and explains the occurrence of outbreaks in schools and nurseries. *Because HAV viremia is transient, blood-borne transmission of HAV occurs only rarely. Waterborne epidemics may occur in developing countries under unsanitary conditions; the incidence of infectious particles in the water supply may exceed 35%, and outbreaks may be falling within acceptable limits. Among developed countries, sporadic infections may be contracted from consumption of shellfish (oysters, mussels, clams), which concentrate the virus from seawater contaminated with HAV. Outbreaks of HAV caused by consumption of shellfish contaminated with HAV caused outbreaks of the disease in the United States in 2003, in*



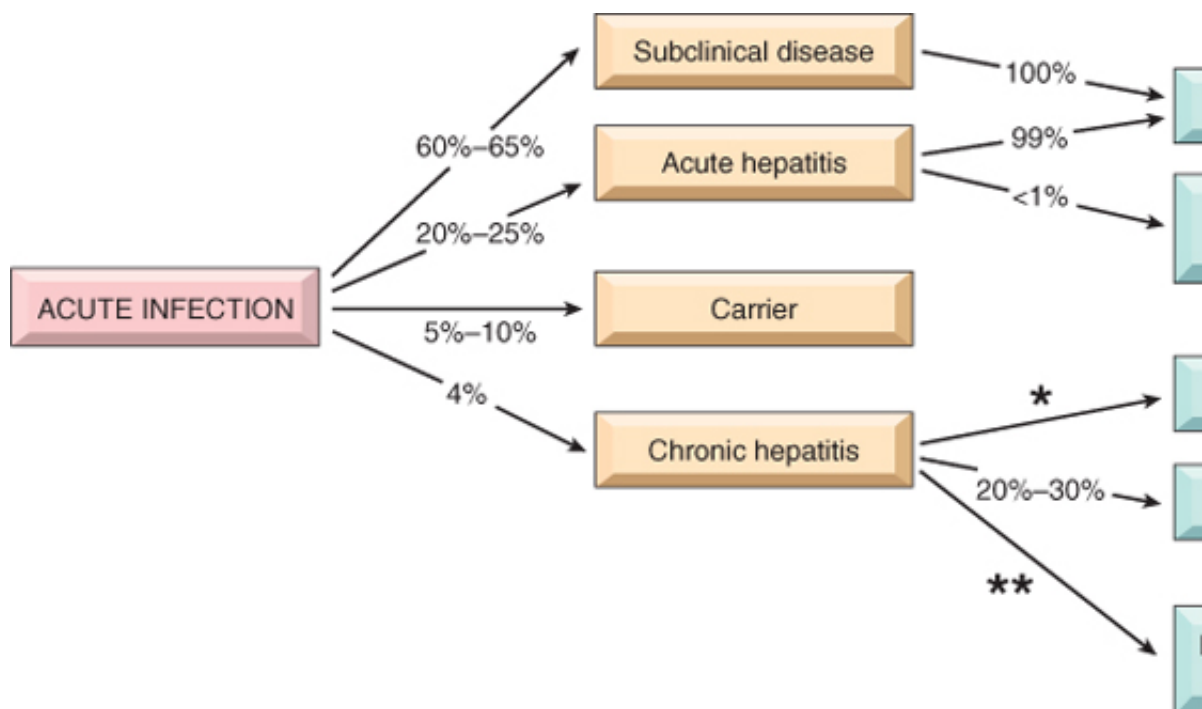


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Figure 16-5 The sequence of serologic markers in acute hepatitis A infection. HAV,

HAV is a small, nonenveloped, single-stranded RNA picornavirus. It reaches the liver from the intestine, infects hepatocytes, and is shed in the bile and feces. The virus itself does not seem to be toxic to hepatocytes, and the damage to the liver is thought to result from T cell-mediated damage of infected hepatocytes. As depicted in Figure 16-5, immunoglobulin M (IgM) anti-HAV appears in blood at the onset of symptoms. Detection of anti-HAV IgM antibody is the best diagnostic test for acute hepatitis A. This antibody persists beyond convalescence and is the primary defense against reinfection. However, IgG anti-HAV, and therefore the presence of this type of antibody is inferred from the difference between the two. In the United States, the prevalence of seropositivity increases gradually with age, reaching 50% by age 60. The major causes of hepatitis A include (1) hygienic measures focused on the disposal of human wastes and personal hygiene, (2) passive immune serum globulin for individuals exposed to the virus or those traveling to high-exposure areas, and (3) using a virus-inactivated vaccine.

### Hepatitis B Virus (HBV)

HBV can produce (1) acute hepatitis with recovery and clearance of the virus, (2) nonprogressive disease ending in cirrhosis, (3) fulminant hepatitis with massive liver necrosis, and (4) an asymptomatic carrier state. Chronic liver disease is an important precursor for the development of hepatocellular carcinoma. Figure 16-6 shows the potential outcomes of these outcomes.

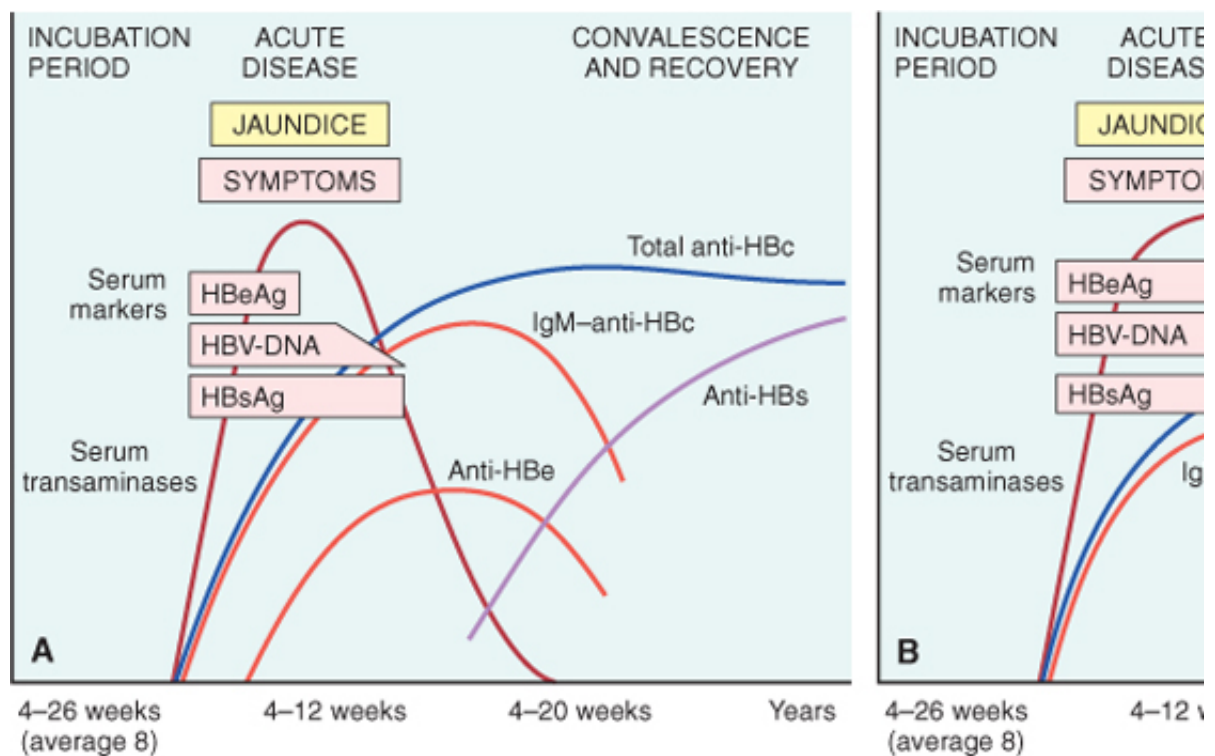


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Figure 16-6 The potential outcomes of hepatitis B infection in adults, with their approximate annual frequencies in the United States. \*The risk of cirrhosis from chronic hepatitis is 0.5-1% per year; \*\*The risk of hepatocellular carcinoma is 0.02% per year for chronic hepatitis B developed.

Globally, liver disease caused by HBV is an enormous problem, with an estimated worldwide carriage estimated that HBV will infect more than 2 billion of the individuals alive today at some point in the live in Asia and the Western Pacific rim, where prevalence of chronic hepatitis B is more than 10% approximately 185,000 new infections per year. HBV remains in blood during the last stages of a and during active episodes of acute and chronic hepatitis. It is also present in all physiologic and of stool. HBV is a hardy virus and can withstand extremes of temperature and humidity. Thus, when primary vehicles of transmission, virus may also be spread by contact with body secretions such as milk, and pathologic effusions. In endemic regions, vertical transmission from mother to child during transmission. In areas of low prevalence, horizontal transmission via transfusion, blood products, health care workers, intravenous drug abuse, and sexual transmission (homosexual or heterosexual) for HBV infection. In one-third of patients the source of infection is unknown. HBV infection in adults transmission produces a high rate of chronic infection.

HBV is a member of the Hepadnaviridae, a group of DNA-containing viruses that cause hepatitis. It does not involve the integration of the virus in the DNA of the host cell, but integrated HBV is frequent. Viruses generally have large deletions and rearrangements and usually become inactive. The genomic circular DNA molecule of 3200 nucleotides that encodes:

The pre-core/core region of a nucleocapsid "core" protein (*HBcAg*, hepatitis B core antigen) and *HBeAg* (hepatitis B "e" antigen). *HBcAg* is retained in the infected hepatocyte; *HBeAg* is secreted into the blood. Envelope glycoprotein (*HBsAg*, hepatitis B surface antigen) is secreted into the blood in massive amounts. Blood *HBsAg* is immunogenic and can be visualized. *HBV* has a *reverse transcriptase* with reverse transcriptase activity (genomic replication takes place through an RNA intermediate). In this process mutant viral genomes are frequently generated. *HBV-X* protein, which has a role in the causation of hepatocellular carcinoma by regulating p53 degradation and



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Figure 16-7 The sequence of serologic markers in acute hepatitis B infection. **A**, Resolution of active infection. **B**, Progression to chronic infection. Abbreviations.

After exposure to the virus, there is a long 45- to 160-day, (average 120 days) asymptomatic incubation period followed by an acute disease lasting many weeks to months. The natural course of acute disease can be followed by the following markers:

HBsAg appears before the onset of symptoms, peaks during overt disease, and then declines over several months. Anti-HBs antibody does not rise until the acute disease is over and is usually not detectable until several months after the disappearance of HBsAg. Anti-HBs may persist for life, conferring protective immunity. Vaccination strategies using noninfectious HBsAg, HBeAg, HBV-DNA, and DNA polymerase all signify active viral replication. Persistence of HBeAg is an important indicator of continued viral replication and probable progression to chronic hepatitis. The appearance of anti-HBe antibodies implies the end of the acute phase and the waning of HBeAg. IgM anti-HBc becomes detectable in serum shortly before the onset of symptoms and rises as serum aminotransferase levels (indicative of hepatocyte destruction). Over a period of months, IgM anti-HBc is replaced by IgG anti-HBc. As in the case of anti-HAV, there is no direct assay for IgG anti-HBc, but it can be detected in the face of rising levels of total anti-HBc.

Occasionally, mutated strains of HBV emerge that do not produce HBeAg but are replication competent. In such patients, the HBeAg may be low or undetectable despite the presence of HBV viral load. A second appearance of vaccine-induced escape mutants, which replicate in the presence of vaccine-induced immunity, is associated with a mutation of arginine at amino acid 145 of HBsAg with **glycine**, which significantly alters recognition of HBsAg by anti-HBs.

The host immune response to the virus is the main determinant of the outcome of the infection. The host response during the initial phases of the infection, and a strong response by virus-specific CD4+ and CD8+ T cells are associated with the resolution of acute infection. There are several reasons to believe that HBV does not cause chronic liver disease. Most importantly, many chronic carriers have virions in their hepatocytes with no evidence of cell damage. The persistence of the virus may result from damage to the virus-infected cells by CD8+ cytotoxic T cells. Thus, the immune response to the virus without causing widespread liver damage.

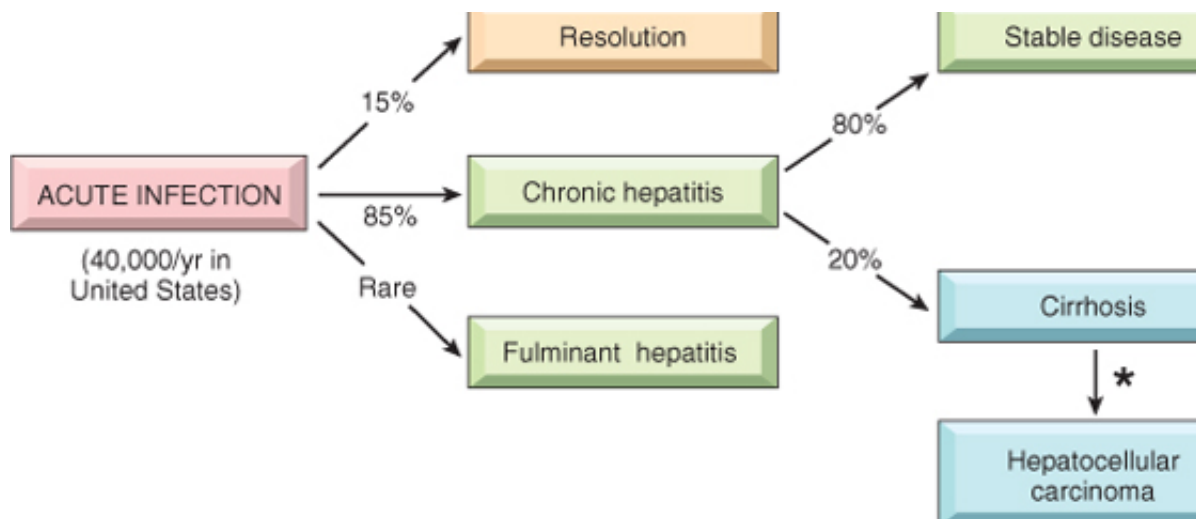
Hepatitis B can be prevented by vaccination and by the screening of donor blood, organs, and tissues. The vaccine is purified HbsAg produced in yeast. Vaccination induces a protective anti-HBs antibody response in infants, children, and adolescents. Universal vaccination has had notable success in Taiwan and Gambia, but unfortunately, it has not been successful in the United States.

### **Hepatitis C Virus (HCV)**

HCV is also a major cause of liver disease. The worldwide carrier rate is estimated at 175 million (range 0.1% to 12%, depending on the country). Persistent chronic infection exists in 3 to 4 million people (range 0.1% to 12%, depending on the country). The number of newly acquired HCV infections per year dropped from 180,000 in the mid-1980s to 10,000 in the mid-1990s. This welcome change resulted from the marked reduction in transfusion-associated hepatitis C (a decline of infections in intravenous drug abusers (related to practices motivated by fear of human immunodeficiency virus (HIV) infection). However, the death rate from HCV will continue to climb for 20 to 25 years, because of the delayed recognition of the disease and liver failure. *The major route of transmission is through blood inoculation, with intravenous drug use being the most common route in the United States.* Transmission via blood products is now fortunately rare, accounting for only 1% of cases. Occupational exposure among health care workers accounts for 4% of cases. The rates of sexual transmission are low. Sporadic hepatitis of unknown source accounts for 40% of cases. *HCV infection has a high rate of progression to chronic disease and eventual cirrhosis (Fig. 16-8). Hepatitis C and chronic alcoholism are the two major causes of liver failure in the Western world, and hepatitis C is the condition that most frequently requires liver transplantation in the United States.*

HCV is a positive-sense single-stranded RNA virus belonging to Flaviviridae, a class of viruses that includes the agents of dengue fever and yellow fever. It contains highly conserved 5'- and 3'-terminal regions that encode structural and nonstructural proteins. Based on the genetic sequence, there are at least six major genotypes. Moreover, because of the poor fidelity of RNA replication, an infected person may carry multiple quasi-species. The relationships between quasi-species development and disease progression are being studied. The multiplicity of quasi-species is associated with worst prognosis. In any case, this variability seriously complicates the development of a vaccine.





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Figure 16-8 The potential outcomes of hepatitis C infection in adults, with their approximate annual frequencies in for newly detected infection; because of the decades-long lag time for progression from acute infection to cirrhosis about 10,000 per year and is expected to exceed 22,000 deaths per year by 2008. \*The risk of hepatocellular carcinoma is increased in patients with cirrhosis.

The incubation period for hepatitis C ranges from 2 to 26 weeks, with a mean of 6 to 12 weeks. It is asymptomatic in 75% of individuals and is easily missed. Thus, not much information is available. It is not detectable in blood for 1 to 3 weeks and is accompanied by elevations in serum aminotransferase. When antibodies develop within weeks to a few months, they *do not confer effective immunity* (Fig. 16-9). CD4<sup>+</sup> and CD8<sup>+</sup> cells are associated with self-limited HCV infections, but it is not known why only some clear HCV infection.

In persistent infection, circulating HCV-RNA is detectable, and aminotransferases show episodic elevations and fluctuating levels. In a small percentage of individuals, aminotransferase levels are persistently low and do not return to normal. Increased enzyme activity may occur in the absence of clinical symptoms, preceding hepatocyte necrosis. *Persistent infection is the hallmark of HCV infection, occurring in 80% to 85% of individuals with acute infection* (see Fig. 16-8). Cirrhosis develops in 20% of persistently infected individuals at the time of diagnosis or may develop over 5 to 20 years. Alternatively, individuals may have documented chronic infection progressing to cirrhosis. Fulminant hepatitis is rare.

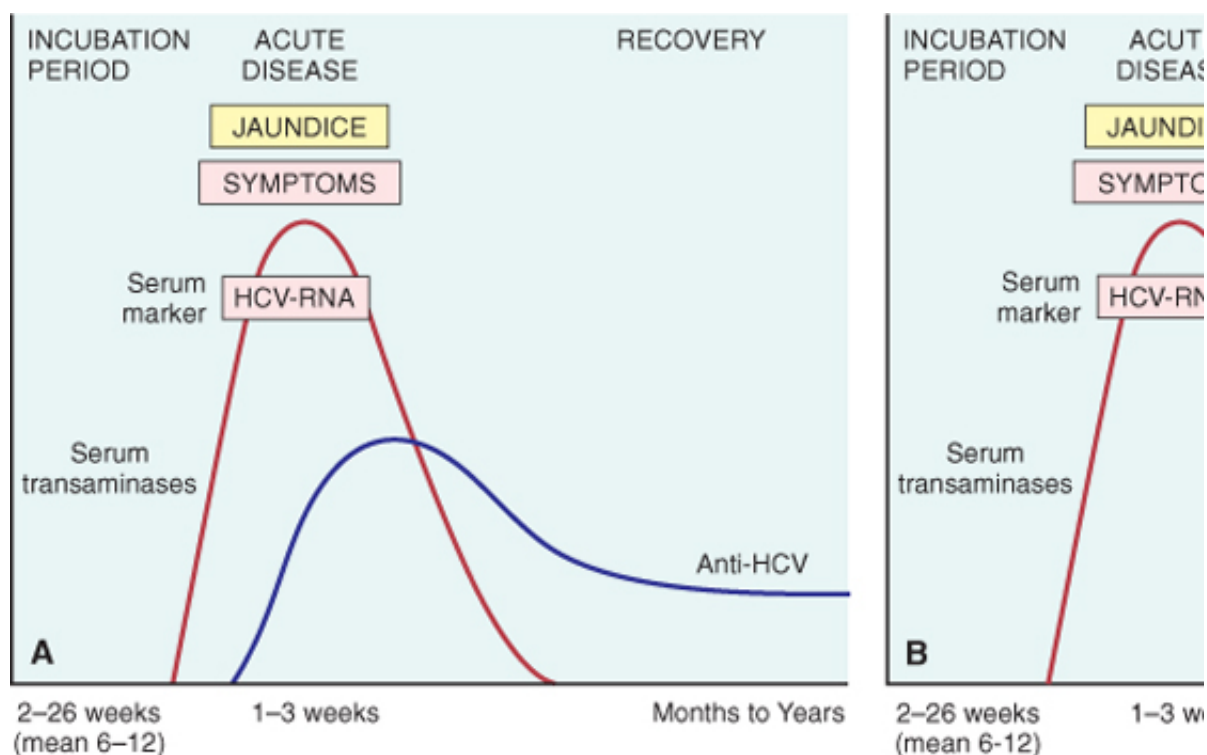
### Hepatitis D Virus (HDV)

Also called hepatitis delta virus, HDV is a unique RNA virus that is replication defective, causing infection only in the presence of HBsAg. Thus, *though taxonomically distinct from HBV, HDV is absolutely dependent on HBV coinfection*. It arises in two settings: (1) acute coinfection after exposure to serum containing both HDV and HBV, or (2) superinfection of an individual who is a chronic carrier of HBV with a new inoculum of HDV. In the first case, HBV infection must become established before development of complete HDV virions. Most coinfecting individuals can clear the viruses and recover, but some become chronic carriers. In most cases, there is an acceleration of hepatitis, progressing to more severe liver disease.

Infection by HDV is worldwide, with prevalence rates ranging from 8% among HBsAg carriers in southern Italy and the Middle East. Surprisingly, HDV infection is uncommon in Southeast Asia and China, areas where HBV is endemic. Periodic epidemic outbreaks have occurred in subtropical areas of Peru, Colombia, and Venezuela, but are largely restricted to drug addicts and individuals receiving multiple transfusions (e.g., hemophiliacs). The prevalence is about 10%.

HDV RNA and the HDV Ag are detectable in the blood and liver just before and in the early days of infection. *HDV antibody is the most reliable indicator of recent HDV exposure*, but its appearance is transient. The presence of HDV and HBV is best indicated by detection of IgM against both HDV Ag and HBcAg (denoting recent infection).

hepatitis arising from HDV superinfection, HBsAg is present in serum; and anti-HDV antibodies (IgG or longer).



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Figure 16-9 Sequence of serologic markers for hepatitis C. **A**, Acute infection with resolution. **B**, Progression to

### Hepatitis E Virus (HEV)

HEV hepatitis is an enterically transmitted, waterborne infection occurring primarily beyond the year 2000 (where it was first documented as caused by fecal contamination of drinking water). Prevalence ranges from 10% to 40% in the Indian population. Epidemics have been reported from Asia, sub-Saharan Africa, and Latin America; it is seen mainly in travelers and accounts for more than 50% of cases of sporadic acute hepatitis. The disease is self-limited; HEV is not associated with chronic liver disease or persistent viremia. However, *the high mortality rate among pregnant women, approaching 20%*. The average incubation period is 40 days (range 2-86 weeks).

HEV is a nonenveloped, single-stranded RNA virus that is best characterized as a calicivirus. A special stain can be used to detect HEV in the cytoplasm of hepatocytes during active infection. Virus can be detected in stools, and anti-HEV is detectable in serum.

### Clinical Features and Outcomes of Viral Hepatitis

A number of clinical syndromes may develop after exposure to hepatitis viruses:

Asymptomatic acute infection: serologic evidence only  
Acute hepatitis: anicteric or icteric  
Chronic hepatitis: progression to cirrhosis  
Chronic carrier state: asymptomatic without apparent disease  
Fulminant hepatitis: hepatic necrosis with acute liver failure

Not all of the hepatotropic viruses provoke each of these clinical syndromes (see Table 16-4). With HAV and HEV, the viruses do not generate a carrier state, and HAV and HEV infections do not progress to chronic hepatitis. With HBV, the progression to chronic disease and development of chronic disease is much more common after HCV infection than for HBV infection.

noninfectious causes, particularly drugs and toxins, can lead to essentially identical syndromes, so diagnosis of viral hepatitis and identification of virus types. Here we present brief summaries of clinical features.

### *Asymptomatic Infection*

Not surprisingly, patients in this group are identified only incidentally on the basis of minimally elevated aminotransferase levels or the fact by the presence of antiviral antibodies.

### *Acute Viral Hepatitis*

Any one of the hepatotropic viruses can cause acute viral hepatitis. Acute infections are easily diagnosed for HCV. Although the following description is mostly based on HBV infections, *acute hepatitis is divided into four phases: (1) an incubation period, (2) a symptomatic preicteric phase, (3) a symptomatic icteric phase, and (4) convalescence.* Peak infectivity, attributed to the presence of circulating virus, occurs in the last asymptomatic days of the incubation period and the early days of acute symptoms. The preicteric phase is characterized by constitutional symptoms. Malaise is followed in a few days by general fatigability, nausea, and loss of appetite. Fever, headaches, muscle and joint aches, vomiting, and diarrhea are inconstant symptoms. About 50% of patients develop a serum sickness-like syndrome consisting of fever, rash, and arthralgias, attributed to circulating immune complexes. The hepatitis-related origin of all these symptoms is suggested by elevated serum aminotransferase levels and a mildly enlarged, tender liver. In some individuals the nonspecific symptoms are more severe, with headache, sometimes accompanied by right upper quadrant pain and tender liver enlargement. Soon after these patients enter the icteric phase, other symptoms begin to abate. The jaundice is caused by hyperbilirubinemia and hence is accompanied by dark-colored urine related to the presence of conjugated bilirubin. In the absence of liver damage and consequent defect in bilirubin conjugation, unconjugated hyperbilirubinemia can also cause jaundice. In the absence of cholestasis, and the retention of bile salts may cause distressing pruritus. An icteric phase is present in all cases of hepatitis A (in children) infected with HAV but is absent in about half the cases involving HBV and is absent in most cases of hepatitis C. Within a few weeks to perhaps several months, the jaundice and most of the other systemic symptoms clear away.

**Chronic Hepatitis** is defined as symptomatic, biochemical, or serologic evidence of continuing or recurrent hepatitis for 6 months, with histologically documented inflammation and necrosis. Although the hepatitis viruses are the most common causes of chronic hepatitis (described later). They include Wilson disease,  $\alpha_1$ -antitrypsin deficiency, (isoniazid<sup>®</sup>,  $\alpha$ -methylidopa, methotrexate), and autoimmunity.

In chronic hepatitis, *etiology rather than the histologic pattern is the most important determinant of outcome.* In particular, HCV is notorious for causing a chronic hepatitis evolving to cirrhosis (see [Fig. 16-8](#)), regardless of histologic features at the time of initial evaluation.

The clinical features of chronic hepatitis are highly variable and are not predictive of outcome. In some cases, the only abnormality is persistent elevations of serum aminotransferase levels. The most common overt symptoms are malaise, loss of appetite, and bouts of mild jaundice. Physical findings are few, the most common being mild erythema, mild hepatomegaly, and hepatic tenderness. Laboratory studies may reveal prolonged prothrombin time, hypergammaglobulinemia, hyperbilirubinemia, and mild elevations in alkaline phosphatase. In hepatitis C and HCV, circulating antibody-antigen complexes produce immune-complex disease, in the form of glomerulonephritis ([Chapter 10](#)) and glomerulonephritis ([Chapter 14](#)). Cryoglobulinemia is found in as many as 50% of patients with hepatitis C. The course is highly variable. Persons with hepatitis C may experience spontaneous remission or may progress to cirrhosis for years. Conversely, some patients have rapidly progressive disease and develop cirrhosis. Causes of death in patients with chronic hepatitis relate to cirrhosis, namely, liver failure, hepatic encephalopathy, portal hypertension, esophageal varices, and hepatocellular carcinoma (see [Figs. 16-6 and 16-8](#)).

### *The Carrier State*

A "carrier" is an individual without manifest symptoms who harbors and therefore can transmit an infectious agent. Carriers are (1) those who harbor one of the viruses but are suffering little or no adverse effects, a liver damage but are essentially free of symptoms or disability. Both constitute reservoirs of infection. In hepatitis B, vertical transmission during childbirth, produces a carrier state 90% to 95% of the time. In hepatitis C, infections acquired in adulthood yield a carrier state. Individuals with impaired immunity are particularly susceptible. The situation is less clear with HDV, although there is a well-defined low risk of posttransfusion hepatitis.

situation is less clear with HDV, although there is a well-defined low risk of posttransfusion hepatitis in conjunction with HBV. HCV can clearly induce a carrier state, which is estimated to affect 0.2% to

### *Fulminant Hepatitis*

A very small proportion of patients with acute hepatitis A, B, or E may develop acute liver failure, and Cases with a more protracted course of several weeks or months are usually referred to as "subacute". Individuals show both massive necrosis and regenerative hyperplasia. As discussed later, drugs can cause hepatic necrosis.

**Table 16-5. Main Morphologic Features of Acute and Chronic Viral Hepatitis**

<b>Acute Hepatitis</b>
Gross: Enlarged, reddened liver; greenish if cholestatic
Parenchymal changes (microscopic)
Hepatocyte injury: swelling (ballooning degeneration)
Cholestasis: canalicular bile plugs
HCV: mild fatty change of hepatocytes
Hepatocyte necrosis: isolated cells or clusters
Cytolysis (rupture) or apoptosis (shrinkage)
If severe: bridging necrosis (portal-portal, central-central, portal-central)
Lobular disarray: loss of normal architecture
Regenerative changes: hepatocyte proliferation
Sinusoidal cell reactive changes
Accumulation of phagocytosed cellular debris in Kupffer cells
Influx of mononuclear cells into sinusoids
Portal tracts
Inflammation: predominantly mononuclear
Inflammatory spillover into adjacent parenchyma, with hepatocyte necrosis
<b>Chronic Hepatitis</b>
Changes shared with acute hepatitis:
Hepatocyte injury, necrosis, apoptosis, and regeneration
Sinusoidal cell reactive changes
Portal tracts
Inflammation:
Confined to portal tracts, or
Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"),
<i>or</i>
Bridging inflammation and necrosis
Fibrosis:
Portal deposition, <i>or</i>
Portal and periportal deposition, <i>or</i>
Formation of bridging fibrous septa
HBV: ground-glass hepatocytes (accumulation of HBsAg)
HCV: bile duct epithelial cell proliferation, lymphoid aggregate formation
<b>Cirrhosis: the End-Stage Outcome</b>

### **Morphology**

The general morphologic features of acute and chronic viral hepatitis are listed in Table 16-5 and presented in Figures 16-10 and 16-11. The morphologic changes in acute and chronic hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions. With severe hepatitis, hepatocyte injury takes the form of diffuse swelling (**ballooning degeneration**), so that the cell is enlarged and contains only scattered wisps of cytoplasmic remnants. An incompetent fi



empty and contains only scattered wisps of cytoplasmic remnants. An inconstant bile plugs in canaliculi and brown pigmentation of hepatocytes. Fatty change is mild with HCV infection. Whether acute or chronic, HBV infection may generate "**ground glass**" (Fig. 16-12): a finely granular, eosinophilic cytoplasm shown by electron microscopy. Large quantities of HBsAg in the form of spheres and tubules. Other HBV-infected hepatocytes have "**sanded**" nuclei, resulting from abundant intranuclear HBcAg.

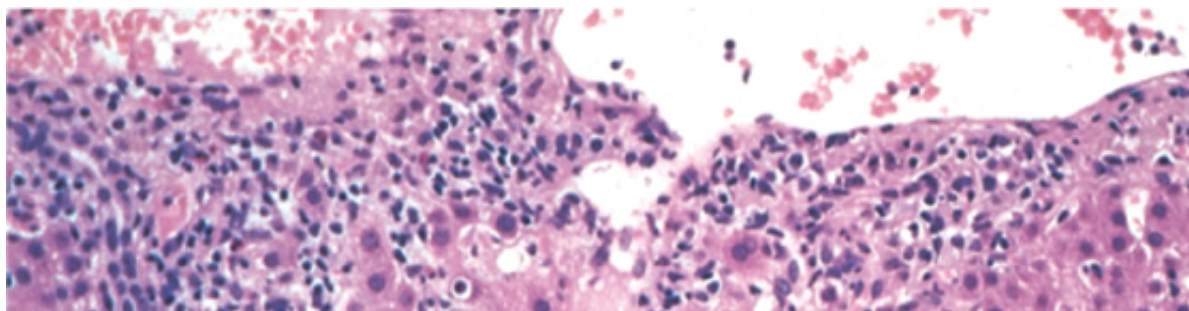
Two patterns of **hepatocyte death** are seen. In the first, rupture of cell membranes and necrotic cells appear to have "dropped out," with collapse of the sinusoidal collagen where the cells have disappeared; scavenger macrophage aggregates mark sites of cell death. A second pattern of cell death, **apoptosis**, is more distinctive. Apoptotic hepatocytes shrink, are eosinophilic, and have fragmented nuclei; effector T cells may be present in the immediate vicinity. Cells also are phagocytosed within hours by macrophages and hence may be difficult to identify. Extensive ongoing apoptosis. In severe cases, confluent necrosis of hepatocytes may be seen. **Necrosis** connecting portal-to-portal, central-to-central, or portal-to-central regions signifies a more severe form of acute hepatitis. Hepatocyte swelling, necrosis, and compression of the vascular sinusoids and loss of the normal, more or less radial arrangement (so-called **lobular disarray**).

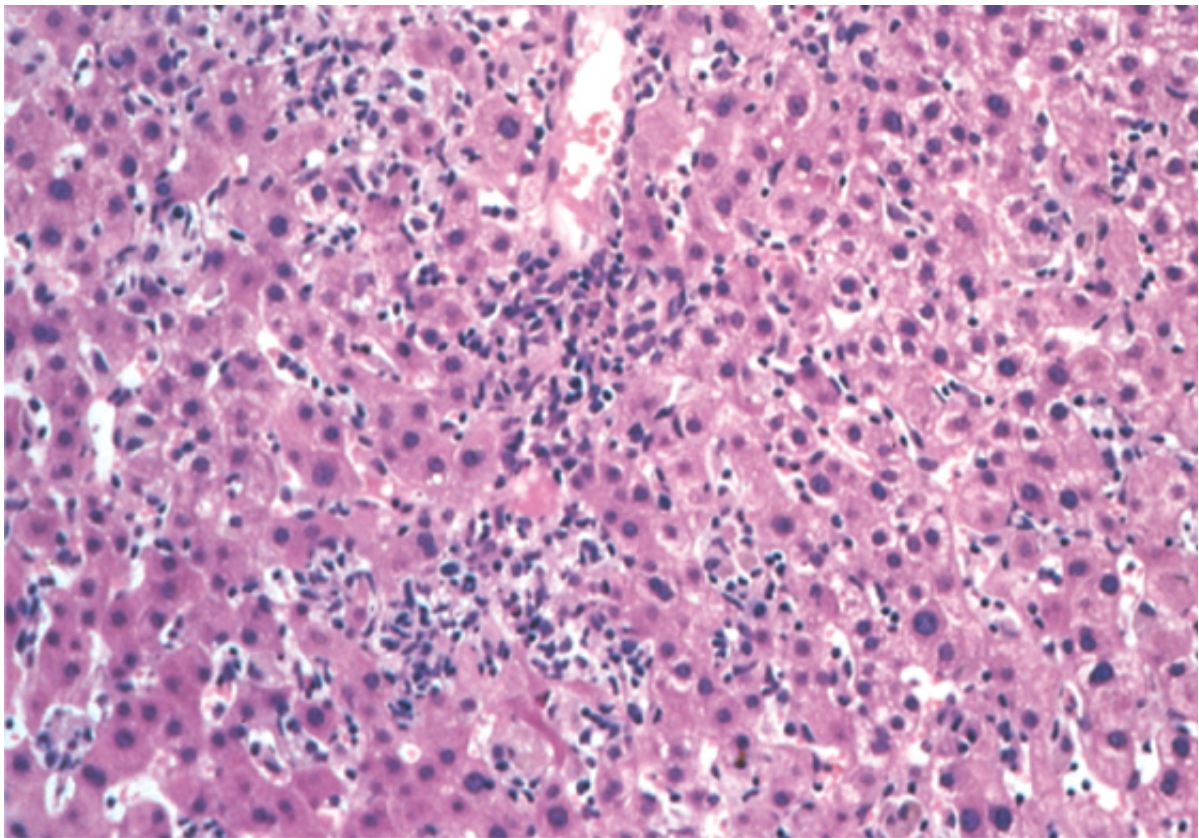
Inflammation is a characteristic and usually prominent feature of acute hepatitis. **Karyorrhexis**, **hyperplasia**, and are often laden with lipofuscin pigment caused by hepatocellular debris. **The portal tracts are usually infiltrated with a mixture of inflammatory cells**. Inflammatory infiltrate may spill over into the parenchyma to cause necrosis of periportal hepatocytes (**interface hepatitis**).

Finally, bile duct epithelium may become reactive and even proliferate, particularly in chronic hepatitis, forming poorly defined ductular structures in the midst of the portal tract inflammation. However, this does not occur.

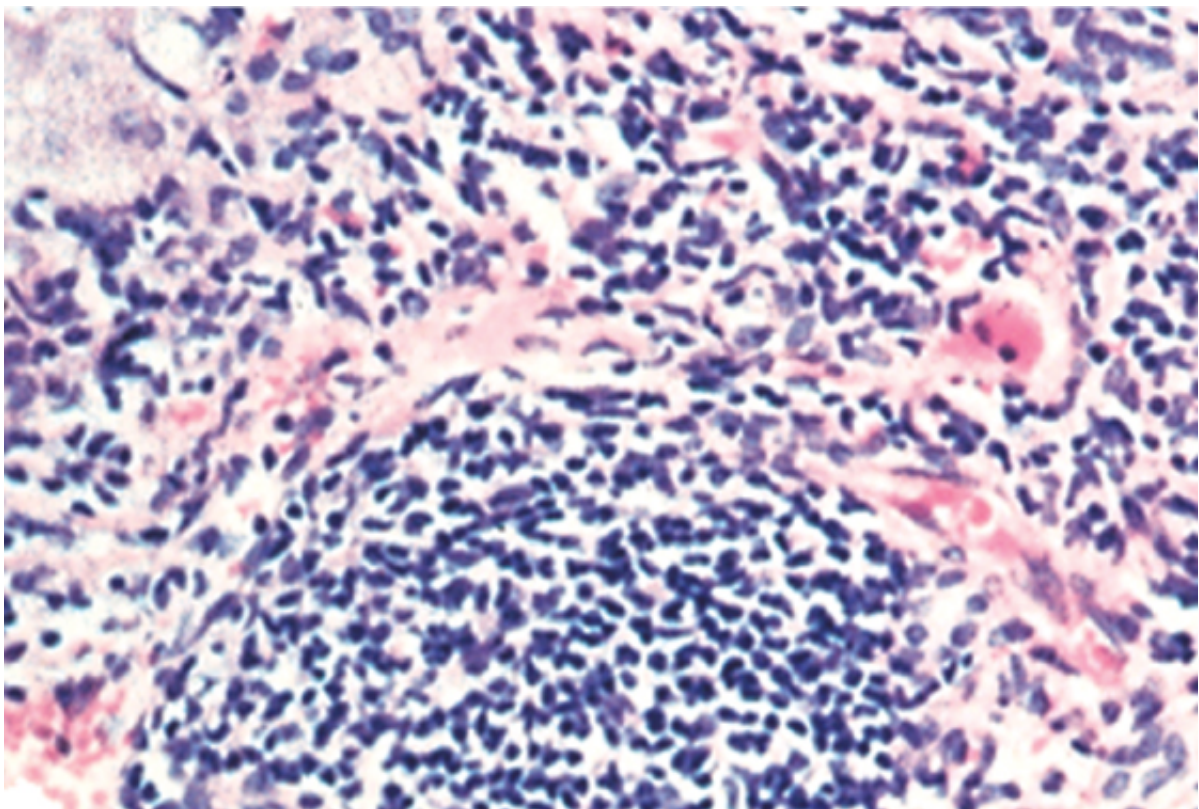
The histologic features of **chronic hepatitis** range from exceedingly mild to severe. Necrosis throughout the lobule may occur in all forms of chronic hepatitis. In the mild form, inflammation is limited to portal tracts and consists of lymphocytes, macrophages, and rare neutrophils or eosinophils. **Lymphoid aggregates** in the portal tract are characteristic of chronic hepatitis. Liver architecture is usually well preserved. Continued **periportal necrosis** are harbingers of progressive liver damage. **The hallmark** of serious liver damage is bridging fibrosis. At first, only portal tracts exhibit increased fibrosis, but with time **periportal fibrosis** by linking of fibrous septa between lobules (**bridging fibrosis**).

**Continued loss of hepatocytes and fibrosis results in cirrhosis, with fibrous bands separating regenerative nodules.** This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad scars (Fig. 16-13). The nodules are typically greater than 3 mm in diameter, earning the term **macronodular cirrhosis**. While such cirrhosis is characteristic of alcoholic liver disease, it is also seen in other etiologies, because hepatotoxins (carbon tetrachloride, mushroom poisons, **acetaminophen**,  $\alpha$ -methyl dopa), and even alcohol (discussed later) may cause cirrhosis. Notably, in about 10% of cases an etiology for the cirrhosis cannot be identified.

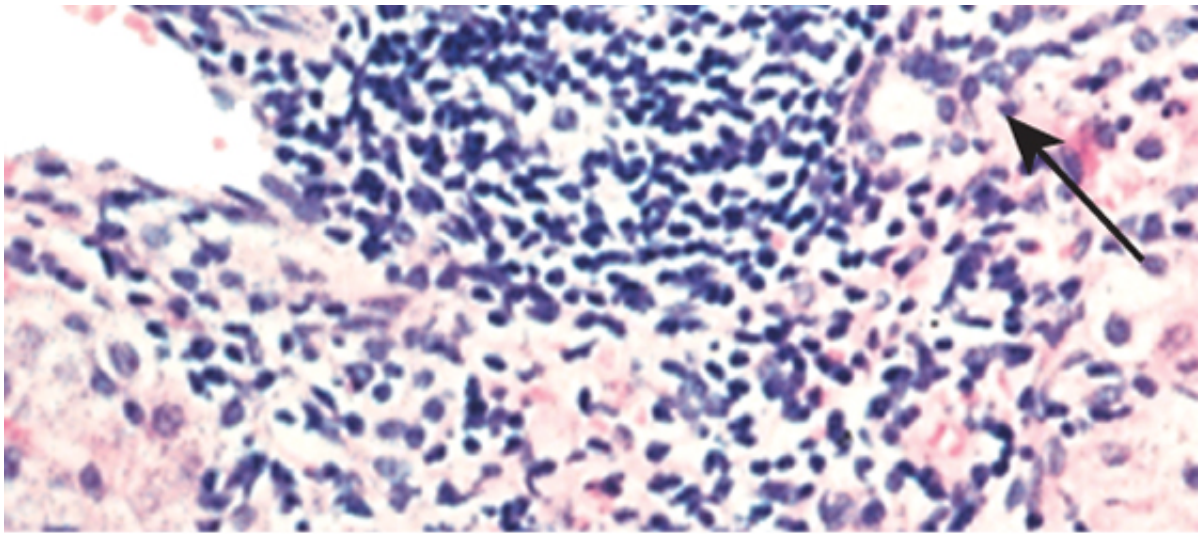




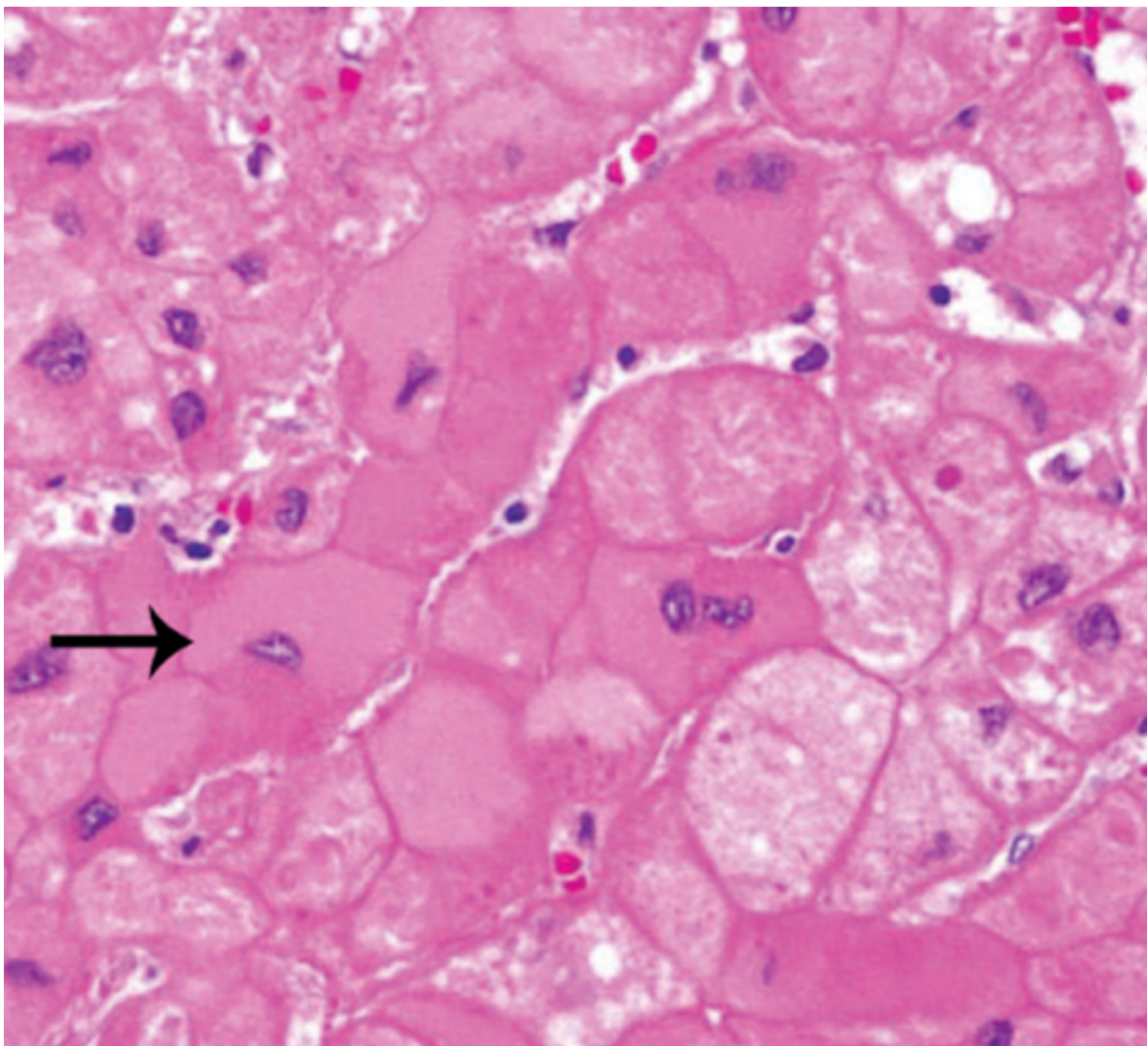
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Figure 16-10 Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in sin

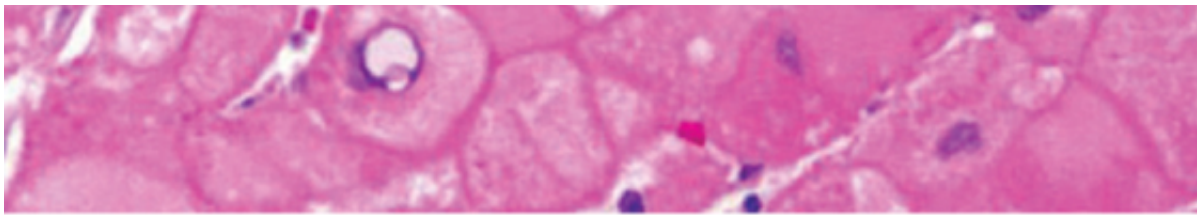






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 Figure 16-11 Chronic hepatitis C showing portal tract expansion with inflammatory cells and fibrous tissue (arrows). Inflammation into the parenchyma (arrowhead). A lymphoid aggregate is present in the





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 Figure 16-12 Ground-glass hepatocytes (arrow) in chronic hepatitis B, caused by accumulation of HBsAg in cytoplasm (H&E stain, 400x magnification, University of Washington, Seattle, Washington.)

## Autoimmune Hepatitis



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 Figure 16-13 Cirrhosis resulting from chronic viral hepatitis. Note the irregular nodularity (gross specimen).

Autoimmune hepatitis is a syndrome of chronic hepatitis in persons with a heterogeneous set of features that are indistinguishable from chronic viral hepatitis. This disease may run an indolent or severe course and may respond dramatically to immunosuppressive therapy. Salient features include:

- Female predominance (70%)
- Absence of serologic markers of a viral infection
- Elevated serum autoantibodies in 80% of cases
- The presence of other forms of autoimmune diseases, such as rheumatoid arthritis, thyroiditis, Sjögren syndrome, and ulcerative colitis.

### *Pathogenesis and Main Clinical Features*



### *Pathogenesis and Main Clinical Features*

Autoimmune hepatitis can be divided into three subtypes on the basis of the autoantibodies, but the clinical management is unclear. Most patients have circulating antinuclear antibodies, anti-smooth microsomal antibody, and anti-soluble liver/pancreas antigen. These antibodies can be detected by immunosorbent assays. The best characterized among these antibodies are smooth muscle antibodies directed against proteins that include actin, troponin, and tropomyosin, and liver kidney microsomal antibodies directed against the cytochrome P-450 system and the UDP-glucuronosyltransferases. The main effectors of cell damage are CD4+ helper cells. Autoimmune hepatitis may present with mild to severe chronic hepatitis. The course is usually dramatic, although a full remission of disease is unusual. The overall risk of cirrhosis, the

### **SUMMARY Hepatitis**

Viral hepatitis is the most common primary liver infection. Autoimmune hepatitis is less frequent. HAV causes a self-limited disease that never becomes chronic; HEV is usually self-limited, but can become chronic, and fulminant disease (1% or less), but the frequency of chronic disease is low. HBV causes acute and chronic hepatitis; the acute phase is often difficult to detect. In chronic disease, the chronic disease may reach 85%; cirrhosis develops in 20% of cases of chronic disease. In chronic hepatitis there is hepatocyte injury and cell death, and inflammation. In chronic hepatitis may show bridging necrosis and fibrosis. Patients with long-term chronic infections are at increased risk of developing hepatocellular carcinomas.

### **Pyogenic Liver Abscesses**

In developing countries liver abscesses are common; most result from parasitic infections, such as (commonly) other protozoal and helminthic organisms. In developed countries parasitic liver abscesses are rare. In immigrants. In the Western world, bacterial abscesses are more common, representing a complication of various organisms reach the liver through one of the following pathways: (1) ascending infection in the biliary tract, (2) vascular seeding, either portal or arterial, predominantly from the gastrointestinal tract (3) direct infection, or (4) a penetrating injury. Debilitating disease with immune deficiency is a common setting for extrinsic abscesses, immunosuppression, or cancer chemotherapy with marrow failure.

Pyogenic (bacterial) hepatic abscesses may occur as solitary or multiple lesions, ranging from millimeters to several centimeters in diameter. They are generally produced by gram-negative bacteria such as *Escherichia coli*. Spread through the arterial or portal system tends to produce multiple small abscesses, whereas (commonly) solitary large abscesses. Gross and microscopic features are those of any pyogenic abscess, containing neutrophils. Occasionally, fungi or parasites rather than bacteria can be identified.

Liver abscesses are associated with fever and, in many instances, with right upper quadrant pain. They are often the result of extrahepatic biliary obstruction. Although antibiotic therapy may control smaller abscesses, surgery is often necessary. Because diagnosis is frequently delayed, particularly in persons with serious coexisting liver disease, liver abscesses range from 30% to 90%. With early recognition and management, as many as 80%





## ALCOHOL- AND DRUG-INDUCED LIVER DISEASE

As the major drug metabolizing and detoxifying organ in the body, the liver is subject to injury from environmental chemicals. Injury may result from direct toxicity, occur via hepatic conversion of a x produced by immune mechanisms, usually by the drug or a metabolite acting as a hapten to conv

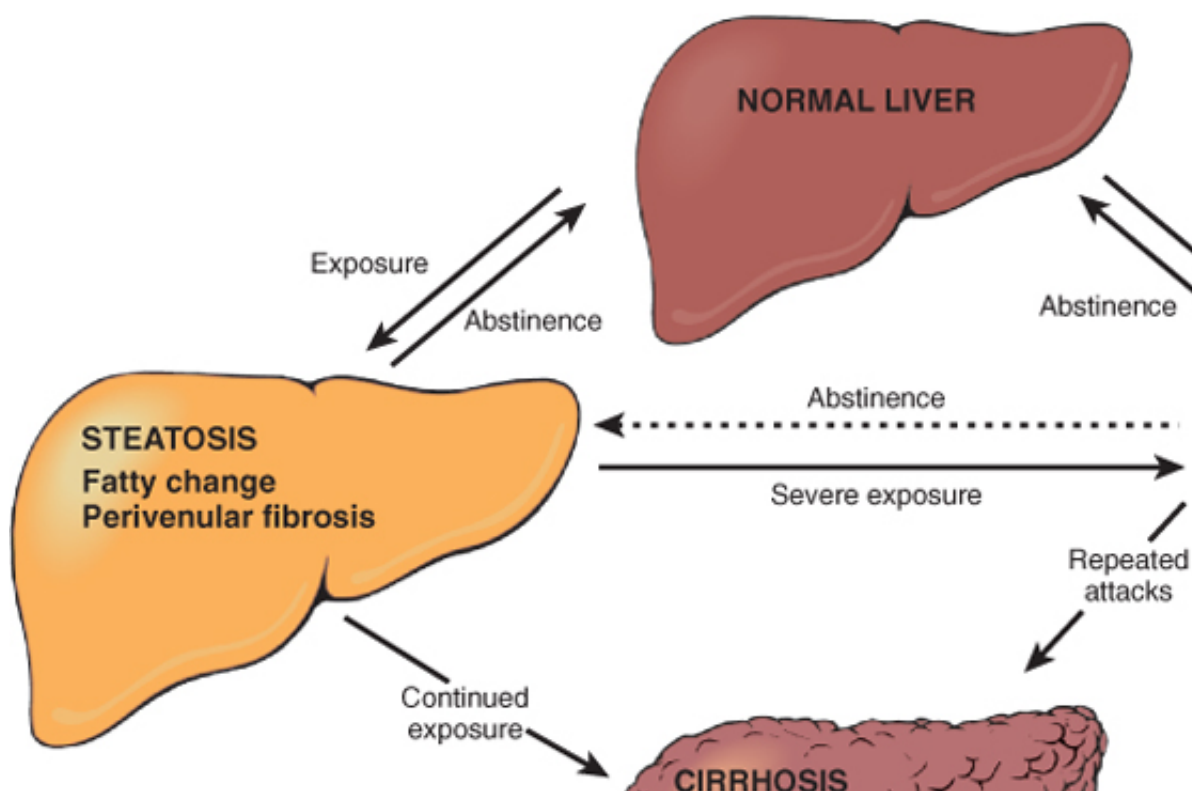
A diagnosis of drug-induced liver disease may be made on the basis of a temporal association of and, it is hoped, recovery on removal of the drug, combined with exclusion of other potential caus agent should always be included in the differential diagnosis of any form of liver disease. By far, th toxic liver injury is alcohol.

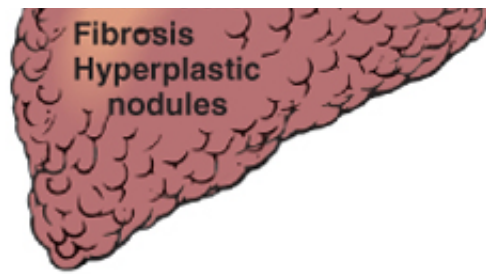
### Alcoholic Liver Disease

Excessive ethanol consumption causes more than 60% of chronic liver disease in most Western c deaths due to cirrhosis. The following statistics attest to the magnitude of the problem in the Unite

More than 10 million Americans are alcoholics. Alcohol abuse causes 100,000 to 200,000 c fifth leading cause of death. Of these deaths, 20,000 are attributable directly to end-stage c automobile accidents. From 25% to 30% of hospitalized patients have problems related to a

Chronic alcohol consumption has a variety of adverse effects ([Chapter 8](#)). Of great impact, howev overlapping, forms of alcoholic liver disease: (1) *hepatic steatosis (fatty liver)*, (2) *alcoholic hepatit to as alcoholic liver disease* ([Fig. 16-14](#)). Ninety to 100% of heavy drinkers develop fatty liver (stei develop alcoholic hepatitis. However, only 8% to 20% of chronic alcoholics develop cirrhosis. Stei independently, and thus, they do not necessarily represent a continuum of changes.





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Figure 16-14 Alcoholic liver disease. The interrelationships among hepatic steatosis, hepatitis, and cirrhosis are shown as different features at the microscopic level.

### Morphology

**Hepatic Steatosis (Fatty Liver).** After even moderate intake of alcohol, small (microscopic) lipid droplets accumulate in hepatocytes. With chronic intake of alcohol, lipid accumulates to the point of forming large, clear macrovesicular globules, compressing and displacing the nucleus to the periphery. This transformation is initially centrilobular, but in severe cases it may involve the entire lobule. Macroscopically the fatty liver of chronic alcoholism is large ( $\leq 4-6$  kg), soft, yellow, and greasy. There is little or no fibrosis at the outset, with continued alcohol intake fibrous tissue eventually replaces the normal architecture, central veins and extends into the adjacent sinusoids. Until fibrosis appears, the fatty liver is reversible if there is abstinence from further intake of alcohol.

**Alcoholic Hepatitis.** This is characterized by the following:

**Hepatocyte Swelling and Necrosis.** Single or scattered foci of cells undergo ballooning and necrosis. The swelling results from the accumulation of fat and water, as well as protein being exported.

**Mallory Bodies.** Scattered hepatocytes accumulate tangled skeins of intermediate filament proteins, visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes. These inclusions are a characteristic but not specific feature of alcoholic liver disease, but they also occur in primary biliary cirrhosis, Wilson disease, chronic cholestatic syndromes, and hepatitis C.

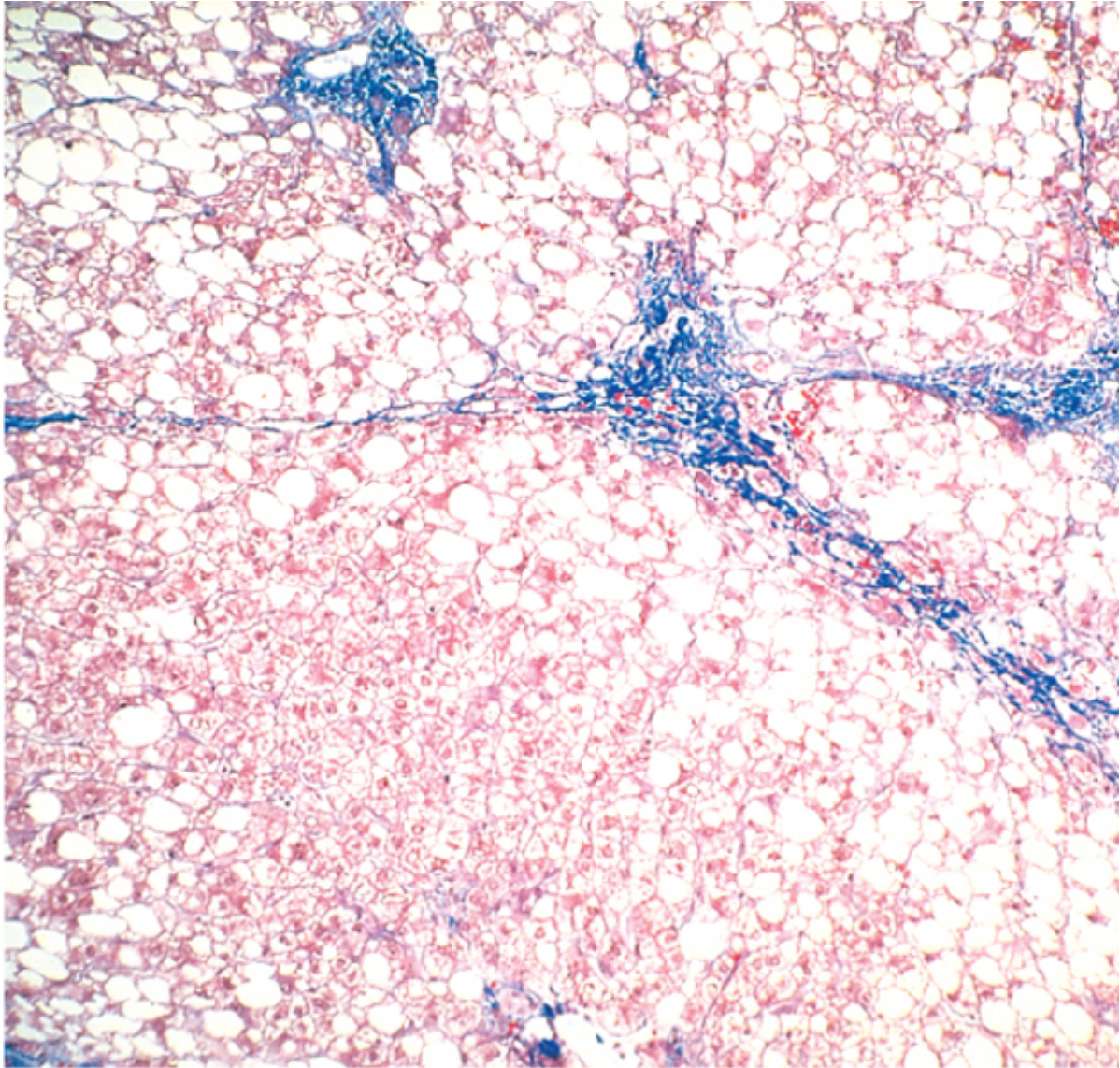
**Neutrophil Infiltration.** Neutrophils permeate the lobule and accumulate around degenerating hepatocytes, particularly those containing Mallory bodies. Lymphocytes and macrophages also infiltrate the parenchyma.

**Fibrosis.** Alcoholic hepatitis is almost always accompanied by a brisk sinusoidal and occasionally periportal fibrosis may predominate, particularly with repeated bouts of disease. In some cases there is cholestasis and mild deposition of hemosiderin (iron) in hepatocytes. Macroscopically, the liver is mottled red with bile-stained areas. Although the liver is enlarged, it often contains visible nodules and fibrosis, indicative of evolving cirrhosis.

**Alcoholic Cirrhosis.** The final and irreversible form of alcoholic liver disease usually develops insidiously. At first the cirrhotic liver is yellow-tan, fatty, and enlarged, usually weighing 1.5-2.0 kg. Over a span of years it is transformed into a brown, shrunken, nonfatty organ, sometimes weighing only 0.5-1.0 kg. Arguably, cirrhosis may develop more rapidly in the setting of alcoholic hepatitis, where the developing fibrous septa are delicate and extend through sinusoids from central veins as well as from portal tract to portal tract. Regenerative activity of entrapped parenchyma generates fairly uniformly sized nodules. Since these nodules tend to be less than 3 mm in diameter, the pattern of cirrhosis is termed **micronodular cirrhosis** (vs. the macronodular cirrhosis of chronic hepatitis). The nodularity eventually becomes more prominent; scattered larger nodules may appear on the surface of the liver (Fig. 16-17). As fibrous septa dissect and subdivide the nodules, the liver becomes more fibrotic, loses fat, and shrinks progressively. Residual regenerating nodules are engulfed by ever wider bands of fibrous tissue, and the liver is converted into a firm, nodular macronodular pattern (Fig. 16-18). Ischemic necrosis and fibrous obliteration of no-

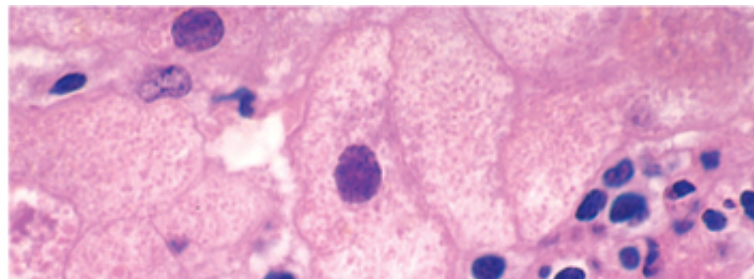


broad expanses of tough, pale scar tissue. Bile stasis often develops; Mallory bodies at this stage. Thus, end-stage alcoholic cirrhosis eventually comes to resemble, microscopically, the cirrhosis developing from viral hepatitis and other causes.

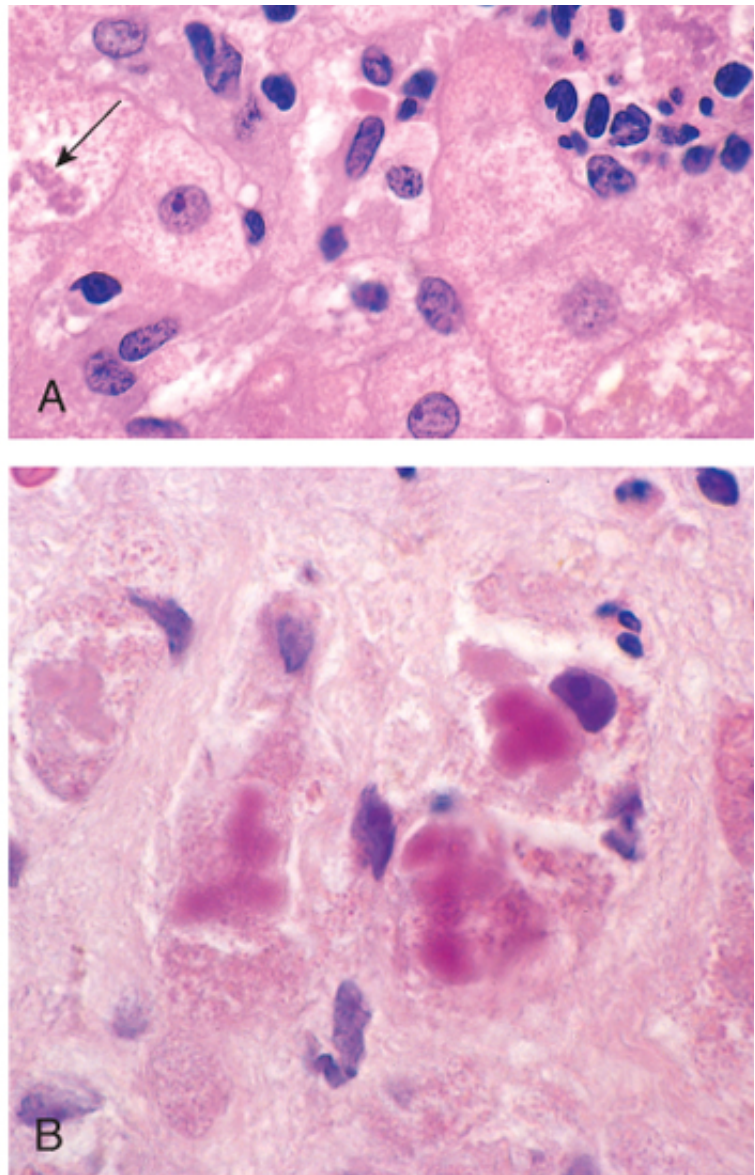


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Figure 16-15 Alcoholic liver disease: macrovesicular steatosis, involving most regions of the hepatic lobule. The intralobular early fibrosis (stained *blue*) is present (Masson trichrome).

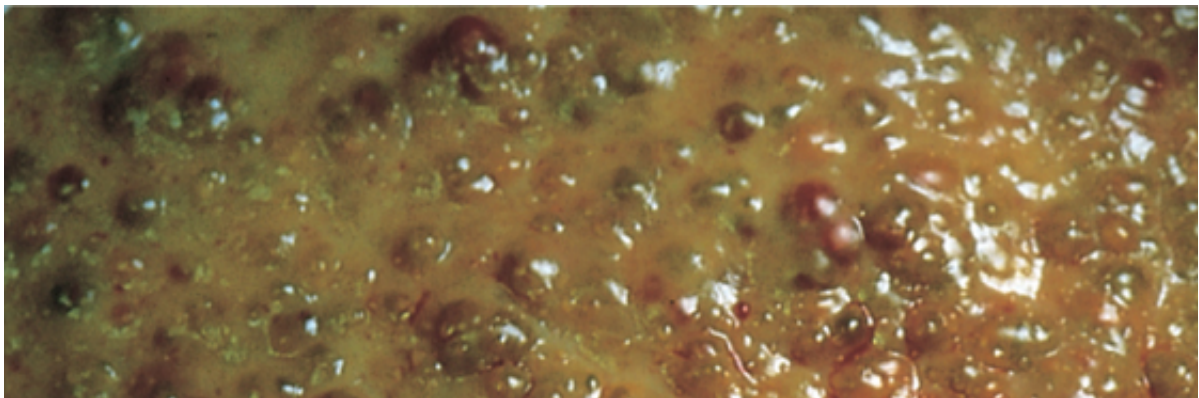
### *Pathogenesis*

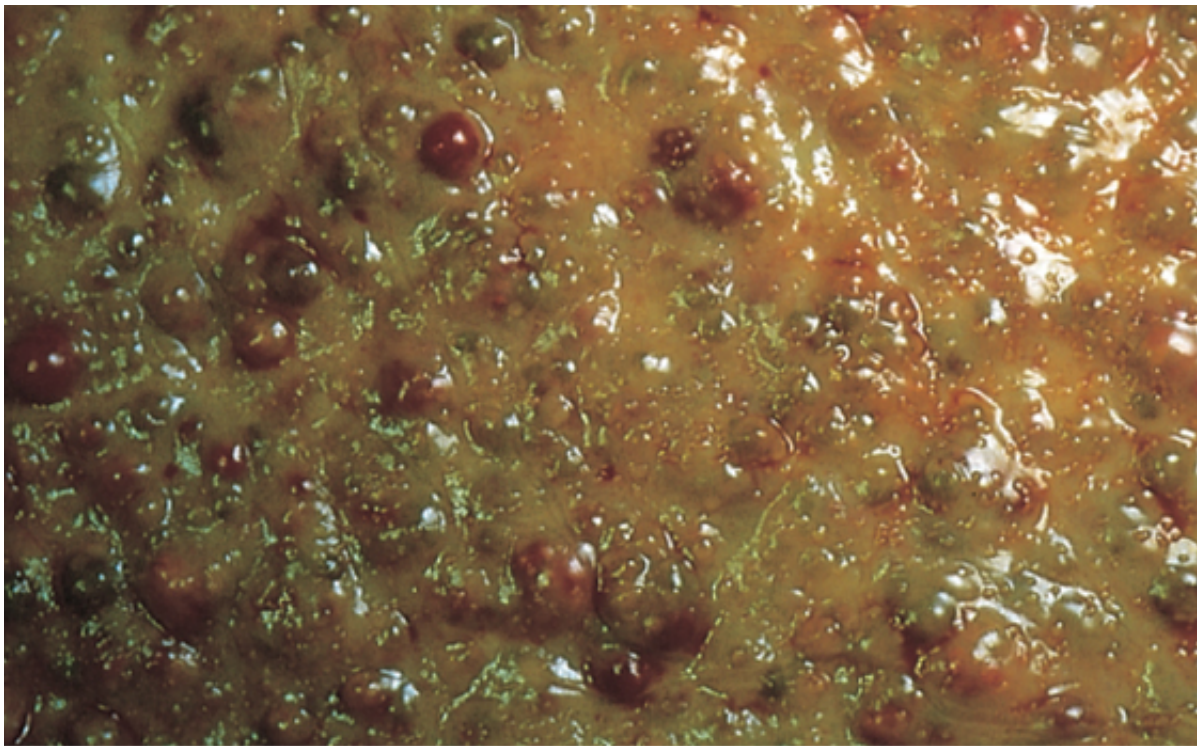






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 Figure 16-16 Alcoholic hepatitis. **A**, The cluster of inflammatory cells marks the site of a necrotic hepatocyte. A (arrow). **B**, Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by

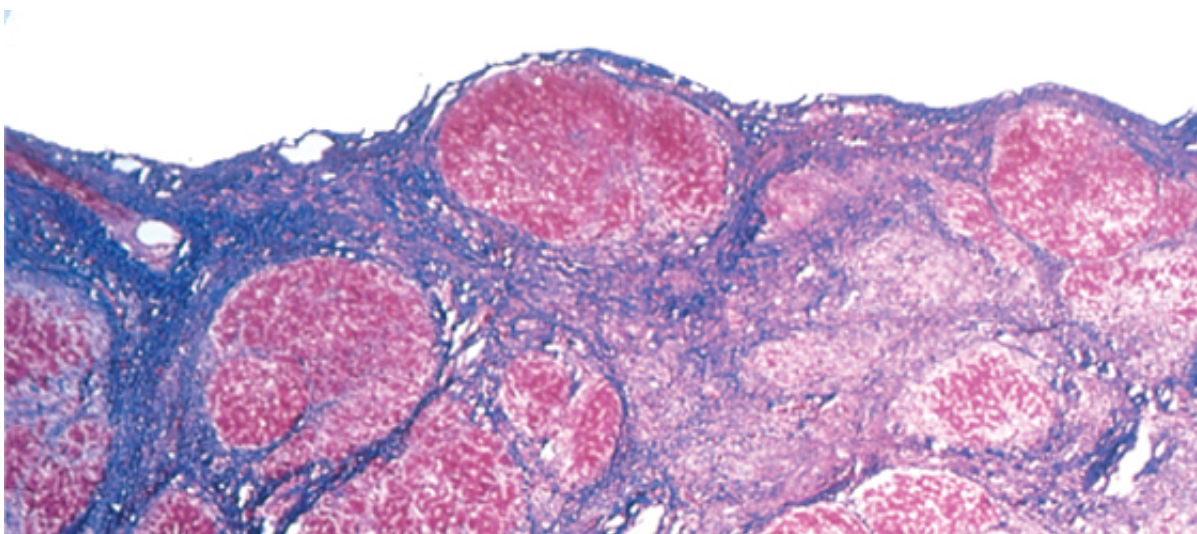




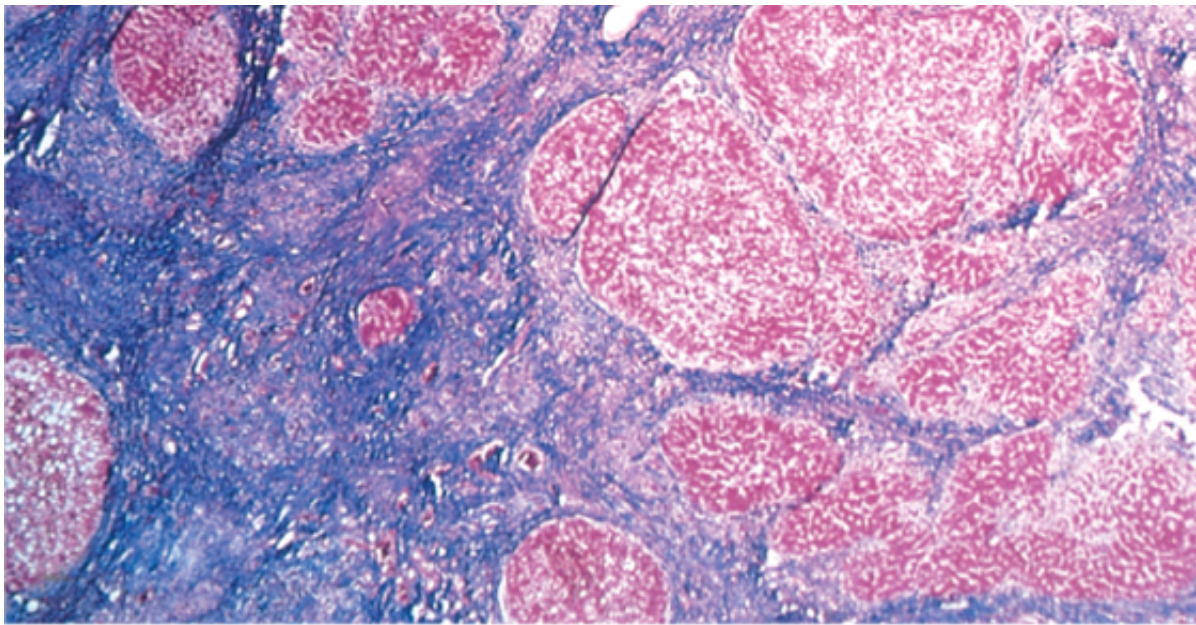
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Figure 16-17 Alcoholic cirrhosis showing the characteristic diffuse nodularity of the surface induced by the underlying regenerative nodules, each 1 to 5 mm in this close-up view. The greenish tint is caused by bile stasis

Short-term ingestion of as much as 80 gm of ethanol per day (8 beers or 7 ounces of 80-proof liquor) can cause acute hepatic changes, such as fatty liver. Chronic intake of 50 to 60 gm/day is considered a borderline level. Factors that may relate to decreased gastric metabolism of ethanol and differences in body composition, women are at greater risk of hepatic injury than are men. It seems that what and how often one drinks may affect the risk of liver damage. Wine carries less risk than beer, and binge drinking causes more liver injury (note that beer binge drinking is the predominant modality of drinking in college student parties). Individual, possibly genetic, susceptibility must exist for liver disease. Susceptibility have been identified. In addition, there is an inconstant relationship between hepatic changes and cirrhosis, which may develop without antecedent evidence of steatosis or alcoholic liver disease. Understanding of the pathogenetic factors influencing liver damage, no "safe" upper limit for alcohol consumption (note the current popularity of red wines for protection against coronary vascular disease).







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Figure 16-18 Alcoholic cirrhosis. Nodules of varying sizes are entrapped in blue-staining fibrous t

The metabolism of alcohol, and ethanol oxidation through the alcohol dehydrogenase and micros discussed in [Chapter 8](#). As mentioned, the induction of cytochrome P-450 by alcohol leads to aug toxic metabolites. In particular, this can accelerate the metabolism of [acetaminophen<sup>®</sup>](#) into highly liver injury even with therapeutic doses of this commonly used analgesic. Here we discuss the del products on hepatocellular function.

*Hepatocellular steatosis* results from (1) the shunting of normal substrates away from catabolism ; generation of excess reduced nicotinamide-adenine dinucleotide by the two major enzymes of alc and acetaldehyde dehydrogenase (generating acetate); (2) impaired assembly and secretion of lip catabolism of fat.

The causes of *alcoholic hepatitis* are uncertain, but the following alterations caused by alcohol are

Acetaldehyde (the major intermediate metabolite of alcohol en route to acetate production) acetaldehyde-protein adduct formation, which may disrupt cytoskeletal and membrane funi organization (as illustrated by the detection of Mallory's hyaline), mitochondrial function, an species are generated during oxidation of ethanol by the microsomal ethanol oxidizing sysl membranes and proteins. Reactive oxygen species are also produced by neutrophils, which

Abnormal cytokine regulation is a major feature of alcoholic hepatitis and alcoholic liver disease ir main effector of injury. The main stimuli for the production of cytokines in alcoholic liver disease (7 oxygen species, mentioned above, and endotoxin (lipopolysaccharide) derived from gut bacteria. free radicals is maximal in the centrilobular region of the parenchyma, this region is most suscepti sinusoidal fibrosis develop in this area of the lobule. Concurrent viral hepatitis, particularly hepatiti disease in alcoholics. The prevalence of hepatitis C in individuals with alcoholic disease is about 3

For unknown reasons, *cirrhosis* develops in only a small fraction of chronic alcoholics. Alcoholic c (disruption of the architecture of the entire liver, and the presence of nodules encircled by bridging hepatitis.

### *Clinical Features*

*Hepatic steatosis* may give rise to hepatomegaly with mild elevation of serum bilirubin and alkaline

be no clinical or biochemical evidence of liver disease. Severe hepatic compromise is unusual. All adequate diet are sufficient treatment. For the occasional heavy drinker, mild hepatic steatosis is

It is estimated that 15 to 20 years of excessive drinking are necessary to develop *alcoholic hepatitis*. Features of alcoholic hepatitis appear relatively acutely, usually after a bout of heavy drinking. Symptoms can be minimal or severe. Between these two extremes are the nonspecific symptoms of malaise, anorexia, and discomfort, tender hepatomegaly, and fever and the laboratory findings of hyperbilirubinemia, elevated serum aminotransferase, and neutrophilic leukocytosis. Serum alanine aminotransferase and aspartate aminotransferase are elevated to 1000 U/mL. The outlook is unpredictable; each bout of hepatitis carries about a 10% to 20% risk of death. In about one-third of patients within a few years; alcoholic hepatitis also may be superimposed on chronic liver disease. After cessation of alcohol consumption, alcoholic hepatitis may clear slowly. However, in some individuals, it progresses to cirrhosis.

The manifestations of *alcoholic cirrhosis* are similar to other forms of cirrhosis, presented earlier. Complications relate to complications of portal hypertension. The stigmata of cirrhosis (e.g., an abdomen grossly distended, spider angiomas, caput medusae) may be the presenting features. Alternatively, a patient may first present with upper gastrointestinal hemorrhage or hepatic encephalopathy. In other cases, insidious onset of malaise, weakness, weight loss, and appearance of jaundice, ascites, and peripheral edema. Laboratory findings reflect the developing liver disease: hyperbilirubinemia, elevated aminotransferase, hyperbilirubinemia, variable elevation of alkaline phosphatase, hypoproteinemia, and anemia. Finally, cirrhosis may be clinically silent, discovered only at autopsy or when complications develop. In chronic alcoholics, alcohol may become a major caloric source, leading to malnutrition and vitamin deficiencies (e.g., thiamine and vitamin B<sub>12</sub>). This is primarily related to chronic gastric and intestinal mucosal damage, and pancreatitis.

The long-term outlook for alcoholics with liver disease is variable. The most important aspect of prognosis is abstinence. Year survival approaches 90% in abstainers who are free of jaundice, ascites, or hematemesis but who continue to imbibe. In the end-stage alcoholic, the immediate causes of death are (1) hepatic failure, (2) upper gastrointestinal hemorrhage, (3) an intercurrent infection (to which these individuals are predisposed), (4) hepatocellular carcinoma, and (5) hepatocellular carcinoma in 3% to 6% of cases.

## Drug-Induced Liver Disease

**Table 16-6. Patterns of Injury in Drug- and Toxin-Induced Hepatic Injury**

Pattern of Injury	Morphologic Findings	Examples of Drugs/Toxins
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive estrogen replacement therapy
Cholestatic hepatitis	Cholestasis with lobular necroinflammatory activity; may show bile duct destruction	Numerous anti-tubercular drugs
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenothiazines
	Submassive necrosis, zone 3	Acetaminophen
	Massive necrosis	Isoniazid, phenothiazines
Steatosis	Macrovesicular	Ethanol, methotrexate, parenteral nutrition
Steatohepatitis	Microvesicular, Mallory bodies	Amiodarone, ethanol
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Methotrexate, chronic alcoholism
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, phenothiazines
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy
	Budd-Chiari syndrome	Oral contraceptives
	Sinusoidal dilatation	Oral contraceptives



	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids
Neoplasms	Hepatic adenoma	Oral contraceptives
	Hepatocellular carcinoma	Thorotrast
	Cholangiocarcinoma	Thorotrast
	Angiosarcoma	Thorotrast, vinyl chloride

From Washington K: Metabolic and toxic conditions of the liver. In Iacobuzio-Donahue CA, Montgomery EA (eds): Gastrointestinal Livingstone; 2005.

Drug-induced liver disease is a common condition that may present as a mild reaction or, much more rarely, as a severe liver injury. A large number of drugs and chemicals can produce liver injury (Table 16-6). Principles of drug and chemical-induced liver injury. Here it suffices to recall that drug reactions may be classified as predictable (intrinsic) reactions or unpredictable (idiosyncratic) reactions. Predictable drug reactions may occur in anyone who accumulates a sufficient dose. Unpredictable drug reactions are determined by the host, particularly the host's propensity to mount an immune response to the antigenic stimulus. The injury may be immediate or take weeks to months to develop. Most idiosyncratic drug reactions are clinically and histologically indistinguishable from chronic viral hepatitis or autoimmune hepatitis, and therefore, the distinction is critical for making the distinction. Among the hepatotoxic agents, predictable drug reactions include tetracycline, antineoplastic agents, *Amanita phalloides* toxin, carbon tetrachloride, and, to a certain extent, alcohol. Idiosyncratic reactions include chlorpromazine (an agent that causes cholestasis in patients with pre-existing liver disease), halothane<sup>®</sup> (which can cause a fatal immune-mediated hepatitis in some patients), and other drugs such as sulfonamides,  $\alpha$ -methyldopa, and allopurinol<sup>®</sup>.

The mechanism of liver injury may be direct toxic damage to hepatocytes (e.g., acetaminophen<sup>®</sup>, carbon tetrachloride, aflatoxin) but also involves a variable combination of toxicity and inflammation with immune-mediated damage. Depending on the drug, the patterns of drug-induced liver injury may include one or more of the following: acute hepatitis, cholestasis, steatosis, steatohepatitis, fibrosis, and vascular lesions. These patterns of injury are characteristic of liver disease, requiring careful analysis to confirm the cause of the injury.

Among drugs that may cause acute liver failure are acetaminophen<sup>®</sup>, halothane<sup>®</sup>, antituberculous drugs, antidepressants, monoamine oxidase inhibitors, industrial chemicals such as carbon tetrachloride, and alcohol. The most common cause (~46% of cases of acute liver failure) is acetaminophen<sup>®</sup> intoxication, a consequence of accidental overdosage. Inadvertent overdosage of acetaminophen<sup>®</sup> is of particular concern in patients who chronically take prescription drugs containing acetaminophen<sup>®</sup> plus an opiate.





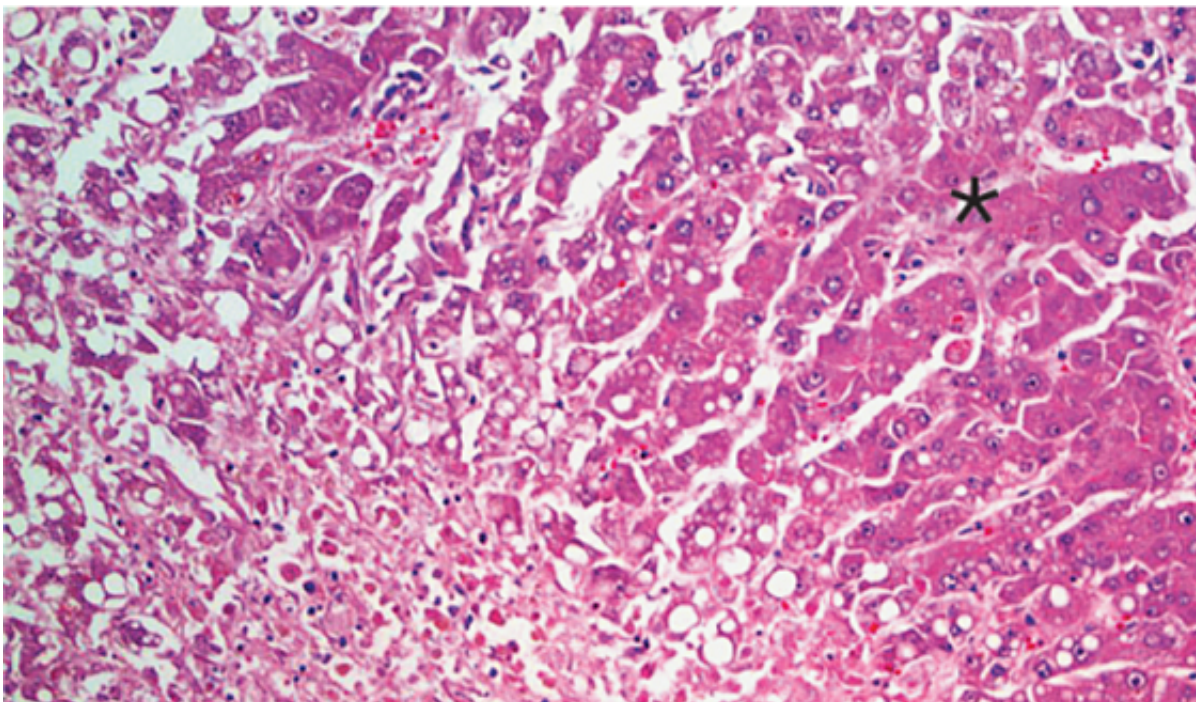
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Figure 16-19 Massive necrosis, cut section of liver. The liver is small (700 gm), bile stained, soft, and congested (Washington, Seattle, Washington.)

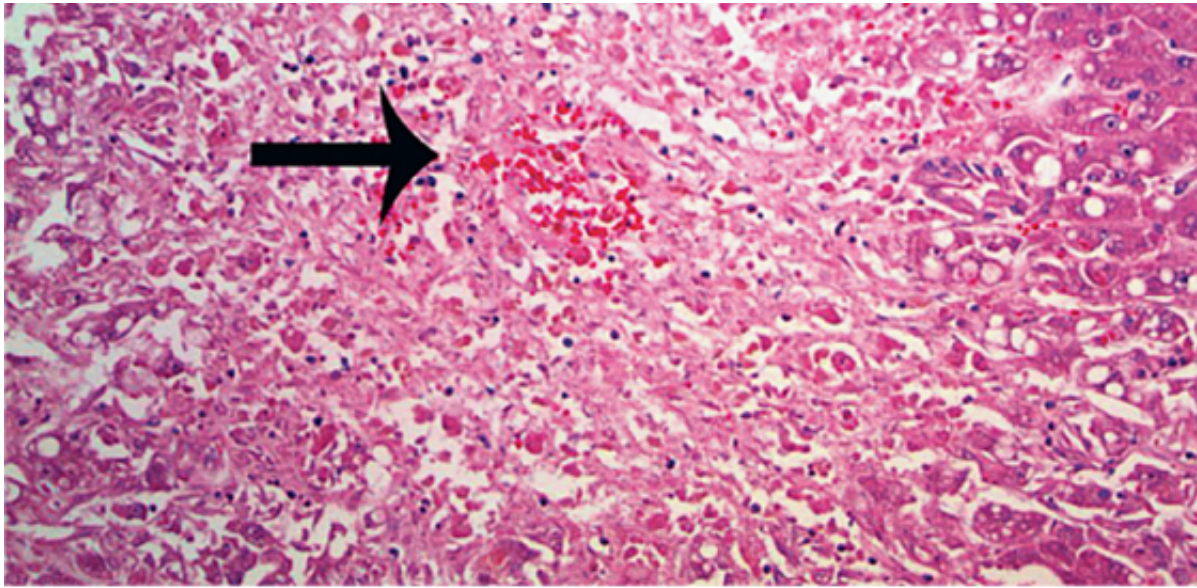
### Morphology

With massive hepatic necrosis, the distribution of liver destruction is extremely cap **may be involved or only random areas are affected.** With massive loss of hepatic mass, the liver may shrink to 500 to 700 gm and become transformed into a limp, red organ covered by a large capsule. On transection (Fig. 16-19), necrotic areas have a muddy red, musty appearance with bile staining. Microscopically, complete destruction of hepatocytes in contiguous lobules is seen, with collapsed reticulin framework and preserved portal tracts. There may be a surprising inflammatory cell reaction (Fig. 16-20). Alternatively, with survival for several days there is a massive infiltration of inflammatory cells to begin the clean-up process.

Patient survival for more than a week permits regeneration of surviving hepatocytes in the form of strings of ductular structures, which mature into hepatocytes. If the portal tracts are preserved, regeneration is orderly and native liver architecture is restored. With massive loss of confluent lobules, regeneration is disorderly, yielding nodular masses of liver cells. In patients with a protracted course of submassive or patchy necrosis, representing a condition called macronodular cirrhosis, as noted earlier.







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 Figure 16-20 Hepatocellular necrosis caused by acetaminophen<sup>®</sup> overdose. Confluent necrosis is seen in the pericentral region, surrounded by inflammation. The residual normal tissue is indicated by the asterisk. (Courtesy of Dr. Matthew Yeh, University of California, San Francisco)

## SUMMARY

### Alcohol and Drug-Induced Liver Disease

Alcoholic liver disease has three main components: hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis; these conditions do not necessarily evolve as a continuum. Consumption of alcohol is considered to be the threshold for the development of alcoholic liver disease. It takes 10 to 15 years of drinking for the development of cirrhosis, which occurs only in chronic alcoholics; alcoholic cirrhosis has the same morphologic and clinical features as cirrhosis caused by viral hepatitis. The multiple pathologic effects of alcohol include cirrhosis and decreased export of lipoproteins, and cell injury caused by reactive oxygen species and cytokines. Drug-induced liver disease may cause multiple patterns of injury, including alcoholic hepatitis, steatosis, necrosis and acute liver failure, sinusoidal obstruction, and neoplasms. Drug-induced chronic hepatitis is clinically and morphologically similar to autoimmune hepatitis.





## METABOLIC AND INHERITED LIVER DISEASE

The most common metabolic liver disease is *nonalcoholic fatty liver disease* (NAFLD). Metabolic liver diseases include hemochromatosis, Wilson disease, and  $\alpha_1$ -antitrypsin deficiency. These diseases are acquired conditions. An additional set of diseases, referred to as neonatal cholestasis, appears in infancy and represents inherited conditions. We first consider NAFLD and then discuss inherited conditions.

### Nonalcoholic Fatty Liver Disease

NAFLD is a common condition, which was first recognized in 1980. As the name denotes, NAFLD develops in individuals who do not drink alcohol. It may present as steatosis (fatty liver) or nonalcoholic steatohepatitis (NASH). The latter is similar to alcoholic hepatitis and involves hepatocyte destruction, parenchymal inflammation, and progressive pericellular fibrosis. NAFLD and NASH are most consistently associated with the following associated variables:

Type 2 diabetes (or family history) Obesity (body mass index  $>30 \text{ kg/m}^2$  in Caucasians and  $>27 \text{ kg/m}^2$  in African Americans) Hypertriglyceridemia, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol

### Pathogenesis and Clinical Features

The combination of insulin resistance with the conditions listed above is known as the *metabolic syndrome*. Diabetes and obesity are the best predictors of severe fibrosis and disease progression. Insulin resistance increases triglycerides in hepatocytes by at least three mechanisms: (1) impaired oxidation of fatty acids, (2) increased fatty acid synthesis, and (3) decrease hepatic secretion of very-low-density lipoprotein cholesterol. Fat-laden hepatocytes produce reactive oxygen species and peroxidation products generated by oxidative stress, which can damage mitochondrial and plasma membranes. As a consequence of oxidative stress or through release from visceral adipose tissue, levels of TNF- $\alpha$  increase, contributing to liver damage and inflammation. The effects of these cytokines are opposite to those in adipose tissue.

NAFLD is the most common cause of incidental elevation of serum transaminases. Most persons with NASH or more advanced NAFLD may also be asymptomatic, but some may have fatigue, malaise, or more severe symptoms of chronic liver disease. Liver biopsy is required for diagnosis. Progression from steatosis to NASH, and from NASH to cirrhosis, seems to be low. Nevertheless, NAFLD is considered a major group of patients with "cryptogenic" cirrhosis. Present therapy of NAFLD is directed toward obesity and insulin resistance. Adiponectins are being investigated as potential therapeutic agents for the treatment of NAFLD.

### Inherited Metabolic Diseases

Although there are a relatively large number of inherited metabolic liver diseases, in this section we discuss only a few selected conditions. They include hemochromatosis, Wilson disease,  $\alpha_1$ -antitrypsin deficiency, and neonatal cholestasis.

#### Hemochromatosis

*Hereditary hemochromatosis* refers to genetic disorders characterized by the excessive accumulation of iron in the parenchymal organs such as the liver and pancreas. There are at least four genes involved in hereditary hemochromatosis. The most common form is an autosomal recessive disease of adult onset caused by a mutation in the HFE gene. Acquired forms of iron accumulation from known sources of excess iron are called *secondary iron overload*. Multiple transfusions, ineffective erythropoiesis (as in  $\beta$ -thalassemia and sideroblastic anemia), and chronic liver disease can also cause iron accumulation.

As discussed in [Chapter 12](#), the total body iron pool ranges from 2 to 6 gm in normal adults; about 25% of which is in hepatocytes. In hereditary hemochromatosis, iron accumulates over the lifetime of an individual. Total iron accumulation may exceed 50 gm, over one-third of which accumulates in the liver.



absorption. Total iron accumulation may exceed 30 gm, over one third of which accumulates in the liver. The clinical features of hemochromatosis are: (1) cirrhosis (all patients), (2) diabetes mellitus (75% to 80% of patients), and (3) skin pigmentation (75% to 80% of patients).

### Pathogenesis

It may be recalled that the total body content of iron is tightly regulated, whereby the limited daily gastrointestinal absorption since there is no excretory pathway for excess absorbed iron. *In hereof, the regulation of intestinal absorption of dietary iron, leading to net iron accumulation of 0.5 to 1 gm per year, is controlled by the HFE gene, responsible for the most common form of this disorder, is called HFE. It is located on chromosome 6 close to the human leukocyte antigen (HLA) gene complex. It encodes a protein that regulates the levels of hepcidin, the iron hormone. The role of HFE in regulating iron uptake is complex and not fully understood. It appears that in less common forms of hereditary hemochromatosis all regulate the levels of hepcidin, the iron hormone. Hepcidin normally down-regulates the efflux of iron from the intestines and macrophages into the plasma and when its levels are reduced there is increased iron absorption. Mice in whom the hepcidin gene is deleted develop severe iron overload, resembling hemochromatosis, and mice that overexpress hepcidin develop severe iron deficiency, thus establishing its role in regulating iron absorption. As might be expected, hepcidin levels are reduced in all currently known forms of hereditary hemochromatosis. The interconnections between function of these various genes and hepcidin synthesis are still being elucidated.*

There are two common mutations in the *HFE* gene associated with hemochromatosis. The first is a tyrosine substitution for cysteine at amino acid 282 (C282Y). The second mutation results in a histidine substitution for aspartate at amino acid 63 (H63D). In Caucasian populations of North European descent, the carrier frequency for the C282Y mutation is 1 in 200. Approximately 80% of hemochromatosis patients are homozygous for the C282Y mutation. Compound heterozygotes for the C282Y/H63D mutation or homozygotes for the H63D mutation account for about 10% of hereditary hemochromatosis patients. The remainder comprise variants of hereditary hemochromatosis.

Hereditary hemochromatosis manifests typically after 20 gm of storage iron has accumulated. It is considered to be directly toxic to tissues by the following mechanisms: (1) lipid peroxidation by iron-catalyzed free radical formation, and (2) direct interactions of iron with DNA. Whatever the actions of iron, they result in nonlethal DNA damage.

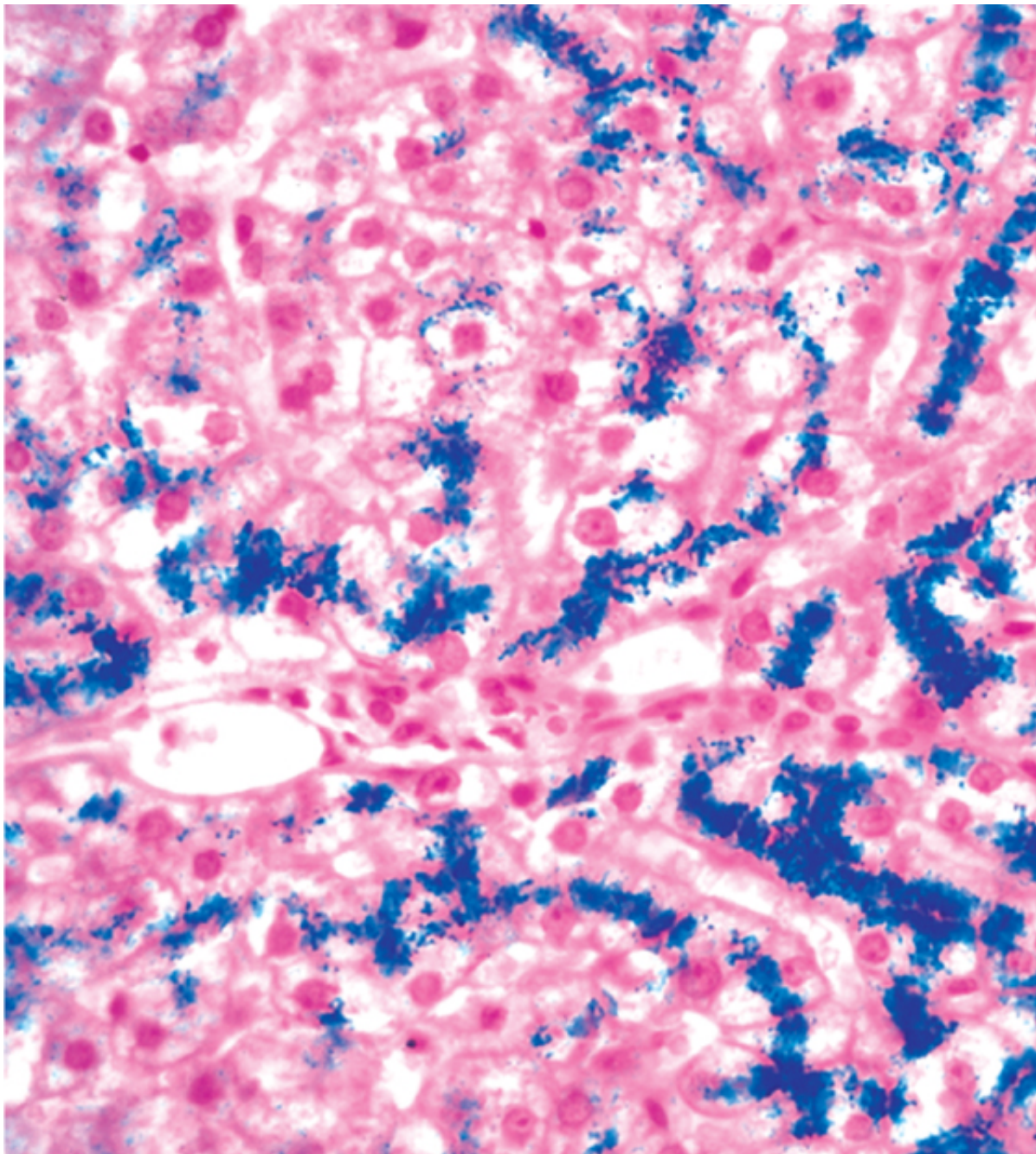
### Morphology

The morphologic changes in hereditary hemochromatosis are characterized principally by the deposition of **hemosiderin** in the following organs (in decreasing order of severity): liver, pancreas, heart, pituitary, adrenal, thyroid and parathyroid glands, joints, and skin; (2) **cirrhosis**; and (3) **skin pigmentation**. In the liver, iron becomes evident first as golden-yellow hemosiderin granules in the hepatocytes, which stain blue with the Prussian blue stain (Fig. 16-21). With increasing severity, there is progressive involvement of the rest of the lobule, along with bile duct epithelium and portal tracts. Iron is a direct hepatotoxin, and inflammation is characteristically absent. The liver is typically slightly larger than normal, dense, and chocolate brown. Fibrous septa develop, leading ultimately to a micronodular pattern of cirrhosis in an intensely pigmented liver.

In normal individuals the iron content of unfixed liver tissue is less than 1000 µg/gm dry weight; with hereditary hemochromatosis exhibit over 10,000 µg/gm dry weight of iron; hepatic iron content in excess of 22,000 µg/gm dry weight are associated with the development of fibrosis and cirrhosis.

The **pancreas** becomes intensely pigmented, has diffuse interstitial fibrosis, and marked atrophy. Hemosiderin is found in the acinar and the islet cells and surrounding fibrous stroma. The **heart** is often enlarged and has hemosiderin granules within the myocardium. Pigmentation may induce a striking brown coloration of the myocardium. A delicate reticular pattern may appear. Although **skin** pigmentation is partially attributable to hemosiderin deposition in the dermis and fibroblasts, most of the coloration results from increased epidermal melanin production. The deposition of these pigments renders the skin slate-gray. With hemosiderin deposition in the joints, chronic synovitis may develop. There is also excessive deposition of calcium pyrophosphate crystals in the articular cartilage and sometimes produces disabling polyarthritides, referred to as chondrocalcinosis. The joints may be small and atrophic but are usually not discolored.

### Clinical Features



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Figure 16-21 Hereditary hemochromatosis. In this Prussian blue-stained histologic section hepatocellular iron appe:

Males predominate (ratio of 5 to 7 : 1) with slightly earlier clinical presentation, partly because phy pregnancy) retards iron accumulation in women. In the most common forms, caused by *HFE* muta the fifth to sixth decades of life. The principal manifestations include hepatomegaly, abdominal pa exposed areas), deranged glucose<sup>R</sup> homeostasis or frank diabetes mellitus from destruction of p: (arrhythmias, cardiomyopathy), and atypical arthritis. In some individuals the presenting complain libido and impotence in men. The classic clinical triad of cirrhosis with hepatomegaly, skin pigmen develop until late in the course of the disease. Death may result from cirrhosis, hepatocellular car iron overload does not remove the risk for development of hepatocellular carcinoma. because of t

iron. The risk of hepatocellular carcinoma development in patients with hemochromatosis is 200-fold

Fortunately, hereditary hemochromatosis can be diagnosed long before irreversible tissue damage. demonstration of very high levels of serum iron and ferritin, exclusion of secondary causes of iron overload. Also important is screening of family members of probands for the causative mutations. The natural history is substantially altered by a variety of interventions, mainly phlebotomy and the use of iron chelators. Patients diagnosed in the subclinical, precirrhotic stage and treated by regular phlebotomy have a normal life expectancy and a mild increase in iron absorption and accumulation.

### **Wilson Disease**

This autosomal recessive disorder of copper metabolism is characterized by the accumulation of copper in various organs, principally the liver, brain, and eye. The genetic defect responsible for Wilson disease is a mutation on chromosome 13, encodes an ATPase metal ion transporter that localizes to the Golgi region of the liver. Several mutations have been detected. The gene for Wilson disease has a frequency of 1 : 200. The incidence of this disease is thus, it is much less common than hereditary hemochromatosis.

Normal copper physiology involves (1) absorption of ingested copper (2-5 mg/day); (2) plasma transport; (3) hepatocellular uptake, followed by incorporation into an  $\alpha_2$ -globulin to form ceruloplasmin; (4) secretion of ceruloplasmin into the circulation where it accounts for 90% to 95% of plasma copper; and (5) hepatic uptake of desialylated, senescent ceruloplasmin, followed by lysosomal degradation and secretion of free copper into bile. In Wilson disease, the first four steps of copper transport to the liver are normal. However, absorbed copper fails to enter the circulation in the form of ceruloplasmin. The elimination of copper from the body is markedly diminished. Defective function of *ATP7B* leads to failure to excrete copper in bile, resulting in *elimination from the body*. The defect apparently also inhibits secretion of ceruloplasmin into the circulation. Copper accumulates progressively in the liver, apparently causing toxic liver injury by (1) promoting the formation of free radicals, (2) displacing other metals in hepatic metalloenzymes. Usually by 5 years of age, the disease becomes manifest. Bound copper spills over into the circulation, causing hemolysis and pathologic changes at other sites, such as the joints, and parathyroid glands. Concomitantly, urinary excretion of copper increases markedly. The diagnosis of Wilson disease is based on a decrease in serum ceruloplasmin, *increase in hepatic copper content*, and a

#### **Morphology**

The liver often bears the brunt of injury in Wilson disease, with hepatic changes ranging from mild to massive damage. **Fatty change** may be mild to moderate, with vacuolated nuclei and occasional hepatocyte focal necrosis. An **acute hepatitis** can mimic acute viral hepatitis, but without the accompanying fatty change. A **chronic hepatitis** resembles chronic hepatitis of viral origin but may show such distinguishing features as fatty change, vacuolated nuclei, and bridging fibrosis. With progression of chronic hepatitis, **cirrhosis** develops. **Massive liver necrosis** is indistinguishable from that caused by viruses or drugs. Excess copper deposition is demonstrated by special stains (e.g., rhodanine stain for copper, orcein stain for collagen). Because copper also accumulates in chronic obstructive cholestasis, and because it is difficult to distinguish Wilson disease from viral- and drug-induced hepatitis, demonstration of an excess of 250  $\mu\text{g/gm}$  dry weight is most helpful for making a diagnosis.

In the **brain**, toxic injury primarily affects the basal ganglia, particularly the putamen, resulting in atrophy and even cavitation. Nearly all patients with neurologic involvement develop **Kayser-Fleischer rings** (green to brown deposits of copper in Descemet membrane of the cornea)-hence the alternative designation of this condition as hepatolenticular degeneration.

### **Clinical Features**

The age at onset and the clinical presentation of Wilson disease are extremely variable, but the diagnosis is usually made in the second or third decade of life. The most common presentation is acute or chronic liver disease. Neuropsychiatric manifestations, such as frank psychosis, or a Parkinson disease-like syndrome, are the initial features in most of the remaining cases. The discovery of Kayser-Fleischer rings or markedly elevated hepatic copper levels in a person with a low serum ceruloplasmin level is diagnostic. Early recognition and long-term copper chelation therapy (as with D-penicillamine) have dramatic effects on the course of the disease.



course.

### **$\alpha_1$ -Antitrypsin (AAT) Deficiency**

AAT deficiency is an autosomal recessive disorder marked by abnormally low serum levels of this AAT is the inhibition of proteases, particularly neutrophil elastase released at sites of inflammation emphysema, because a relative lack of this protein permits the unrestrained activity of tissue-destructive

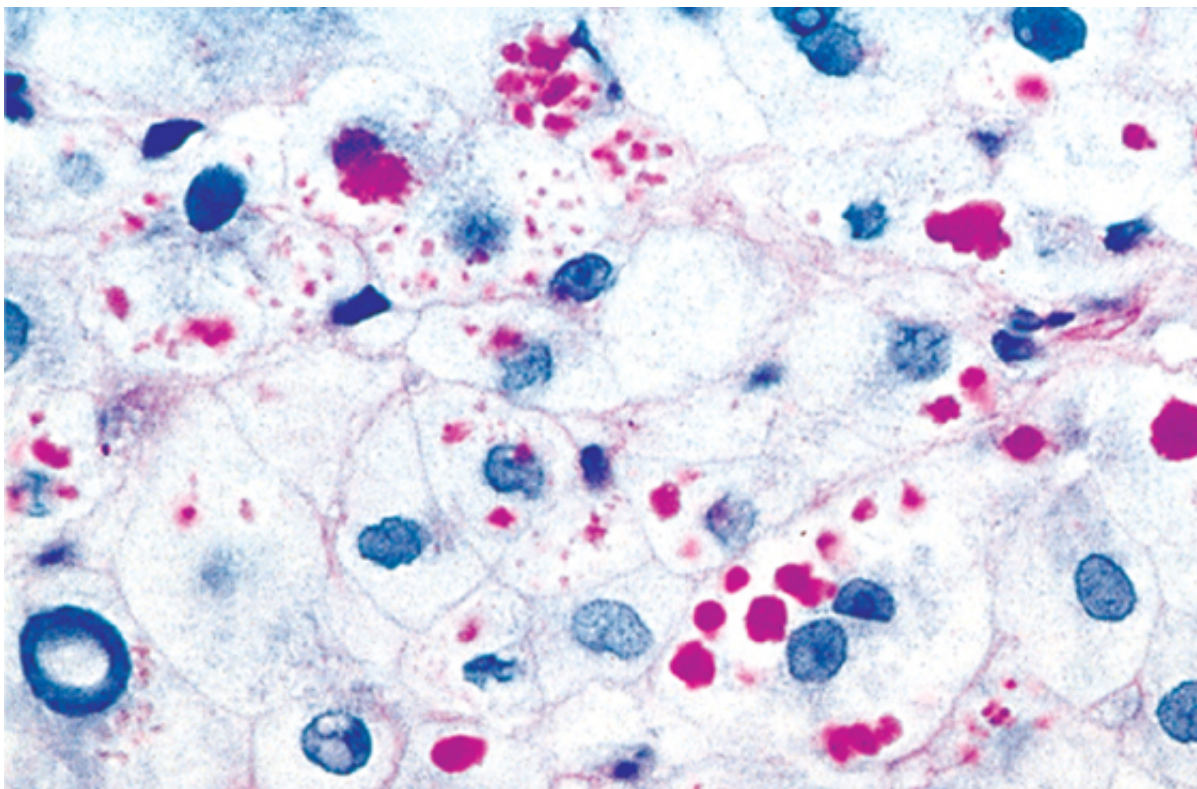
AAT is a small (394-amino acid) plasma glycoprotein synthesized predominantly by hepatocytes. chromosome 14, is very polymorphic, and at least 75 forms have been identified. Most allelic variants have different levels of serum AAT. However, homozygotes for the Z allele (*PiZZ* genotype) have circulating AAT levels. Expression of AAT alleles is autosomal codominant, and consequently *PiMZ* heterozygotes have intermediate levels of AAT. The *PiZ* polypeptide contains a single amino acid substitution that results in misfolding of the protein in the endoplasmic reticulum. Because the mutant protein cannot be secreted by the hepatocyte, it accumulates and undergoes excessive lysosomal degradation. Curiously, all individuals with the *PiZZ* genotype accumulate AAT, and 20% develop significant liver damage. This may be related to a genetic tendency that causes susceptible individuals to degrade accumulated AAT protein within hepatocytes.

#### **Morphology**

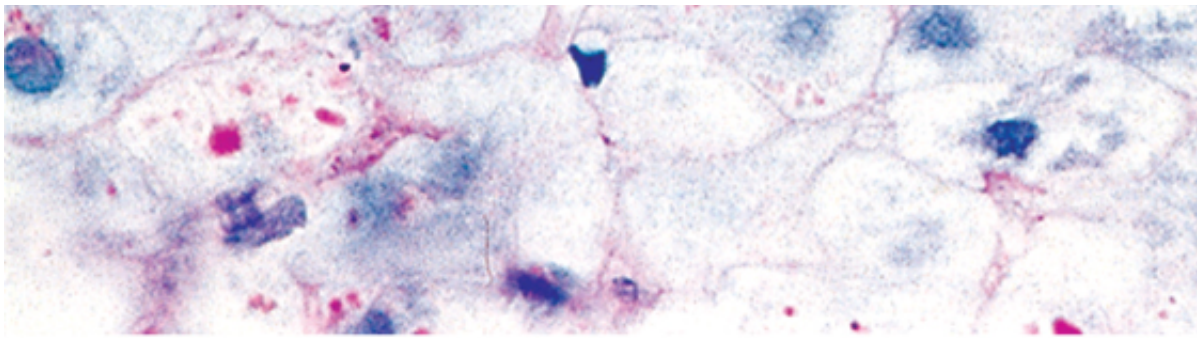
Hepatocytes in AAT deficiency contain round to oval cytoplasmic **globular inclusions** which are strongly positive in a periodic acid-Schiff stain (Fig. 16-22). By electron microscopy, these inclusions have a smooth, and sometimes rough, endoplasmic reticulum. Hepatic injury associated with AAT deficiency may range from marked **cholestasis** with **hepatocyte necrosis** in newborns, to chronic liver disease in adults. A smoldering chronic inflammatory hepatitis or cirrhosis that becomes apparent only in late childhood or adulthood.

#### *Clinical Course*

Among newborns with AAT deficiency, 10% to 20% show cholestasis. In older children, adolescents, and adults, the disease may be related to chronic hepatitis, cirrhosis, or pulmonary disease. The disease may remain silent until late in life. Hepatocellular carcinoma develops in 2% to 3% of *PiZZ* adults, usually, but not always, in the setting of cirrhosis. The treatment for the severe hepatic disease is orthotopic liver transplantation.







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Figure 16-22  $\alpha_1$ -Antitrypsin deficiency. Periodic acid-Schiff stain of liver, highlighting the characteristic red cytoplasmic staining of hepatocytes. (Toronto General Hospital, Ontario, Canada.)

### Neonatal Cholestasis

As mentioned earlier, mild transient elevations in serum unconjugated bilirubin are common in newborns. In the newborn, termed *neonatal cholestasis*, affects approximately 1 in 2500 live births. It is not a specific entity, nor are the disorders necessarily inflammatory. Instead, the finding of "neonatal cholestasis" is a search for recognizable toxic, metabolic, and infectious liver diseases. *Idiopathic neonatal hepatitis* and *neonatal hepatitis*.

Clinical presentation of infants with any form of neonatal cholestasis is fairly typical, with jaundice, hepatomegaly. Variable degrees of hepatic synthetic dysfunction, such as hypoprothrombinemia, the two most common causes of neonatal cholestasis (extrahepatic atresia and idiopathic hepatitis). Definitive treatment of biliary atresia requires surgical intervention, whereas surgery may adversely affect idiopathic neonatal hepatitis. Fortunately, discrimination between these diseases can be made in liver biopsy.

### Reye Syndrome

*Reye syndrome is a rare disease characterized by fatty change in the liver and encephalopathy.* It primarily affects children younger than 4 years of age, typically developing 3 to 5 days after a viral illness. It is accompanied by irritability or lethargy and hepatomegaly. Serum bilirubin levels are essentially normal at this time. Although most patients recover, about 25% progress to death. Serum levels of bilirubin, aminotransferases, and particularly ammonia. Death occurs from progressive liver failure. Survivors of more serious illness may be left with permanent neurologic impairments.

The pathogenesis of Reye syndrome involves a generalized loss of mitochondrial function. Reye syndrome is a prototype of a wide variety of conditions known as "*mitochondrial hepatopathies*." Reye syndrome is often associated with administration during viral illnesses, but there is no evidence that salicylates play a causal role in it. In the United States, the incidence of classic Reye syndrome is less than 1 per million per year, this disorder and "fatty liver" are in the differential diagnosis of postviral disorders in children.

#### Morphology

The key pathologic finding in the **liver** is microvesicular steatosis. Electron microscopy of the liver reveals pleomorphic enlargement and electron lucency of the mitochondrial matrix, loss of cristae and loss of dense bodies. In the **brain**, cerebral edema is usually present. Mitochondrial changes similar to those seen in the liver may develop. Inflammation is absent. There is no evidence of viral infection. **Skeletal muscles, kidneys, and heart** may also show fatty change and mitochondrial alterations, though more subtle than those of the liver.

### SUMMARY

#### Metabolic and Inherited Liver Diseases

## Metabolic and Inherited Liver Disease

The most common metabolic disorder is nonalcoholic fatty liver disease, which is associated with metabolic syndrome and obesity. Nonalcoholic fatty liver disease may develop and progress to nonalcoholic steatohepatitis and finally to cirrhosis. The inherited metabolic diseases include hemochromatosis, Wilson disease,  $\alpha_1$ -antitrypsin deficiency, cholestasis and Reye syndrome. Hemochromatosis is characterized by accumulation of iron in the liver and pancreas. It is caused by a mutation in the *HFE* gene, whose product is involved in iron uptake. Wilson disease is the result of accumulation of copper in the liver, caused by a mutation in the metal ion transporter *ATP7B*.  $\alpha_1$ -antitrypsin deficiency is caused by a mutation in the *AT1A1* gene, leading to reduced production of  $\alpha_1$ -antitrypsin in individuals of *PiZZ* genotype; the main consequences are emphysema caused by increased elastase activity, and liver injury caused by abnormal  $\alpha_1$ -antitrypsin.



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## DISEASES OF THE INTRAHEPATIC BILIARY TRACT

Biliary tract disorders cannot be neatly divided into intrahepatic or extrahepatic, particularly because extrahepatic segments, and extrahepatic biliary disorders may cause secondary changes within the frequently damaged as part of a more general liver disease, as in drug toxicity, viral hepatitis, and transplantation and graft-versus-host disease after bone marrow transplantation). With these caveats, two disorders of bile ducts, primary biliary cirrhosis and primary sclerosing cholangitis, that culminate in biliary cirrhosis is characterized by destruction of intrahepatic bile ducts, and primary sclerosing cholangitis is characterized by destruction of extrahepatic bile ducts. Bile duct disorders initiated primarily in the extrahepatic segment are discussed in the next section.

### Primary Biliary Cirrhosis

Primary biliary cirrhosis is a chronic, progressive, and often fatal cholestatic liver disease, characterized by destruction of bile ducts, portal inflammation and scarring, and the eventual development of cirrhosis and liver failure. *A characteristic feature of this disease is a nonsuppurative destruction of small and medium-sized intrahepatic bile ducts.* In the early lesions there is a dense lymphocyte/plasma cell infiltrate around small bile ductules. Later lesions may also appear. Primary biliary cirrhosis is primarily a disease of middle-aged women, with onset in middle years and peak incidence between 40 and 50 years of age.

#### Pathogenesis and Clinical Course

More than 90% of persons with primary biliary cirrhosis have high titers of antimitochondrial antibody directed against specific domains of mitochondrial acid dehydrogenase enzymes. Despite their characterization, it is not clear why this enzyme domain is the target, and why intrahepatic bile ducts are the targets for these antibodies. Exposure to certain xenobiotics may modify mitochondrial proteins leading to a decrease of immunoreactivity. Nevertheless, it is not known whether exposure to xenobiotics has a role in the pathogenesis of primary biliary cirrhosis.

**Table 16-7. Main Features of Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis**

Parameter	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Age	Median age 50 years (30-70)	Median age 30 years
Gender	90% female	70% male
Clinical course	Progressive	Unpredictable but progressive
Associated conditions	Sjögren syndrome (70%)	Inflammatory bowel disease (70%)
	Scleroderma (5%)	Pancreatitis ( $\leq 25\%$ )
	Thyroid disease (20%)	Idiopathic fibrosing diseases (retroperitoneal)
Serology	95% AMA positive	0% to 5% AMA positive (low titer)
	20% ANA positive	6% ANA positive
	60% ANCA positive	82% ANCA positive
Radiology	Normal	Strictures and beading of large bile ducts
Duct lesion	Florid duct lesion; loss of small ducts	Concentric periductal fibrosis; loss of ducts

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody.

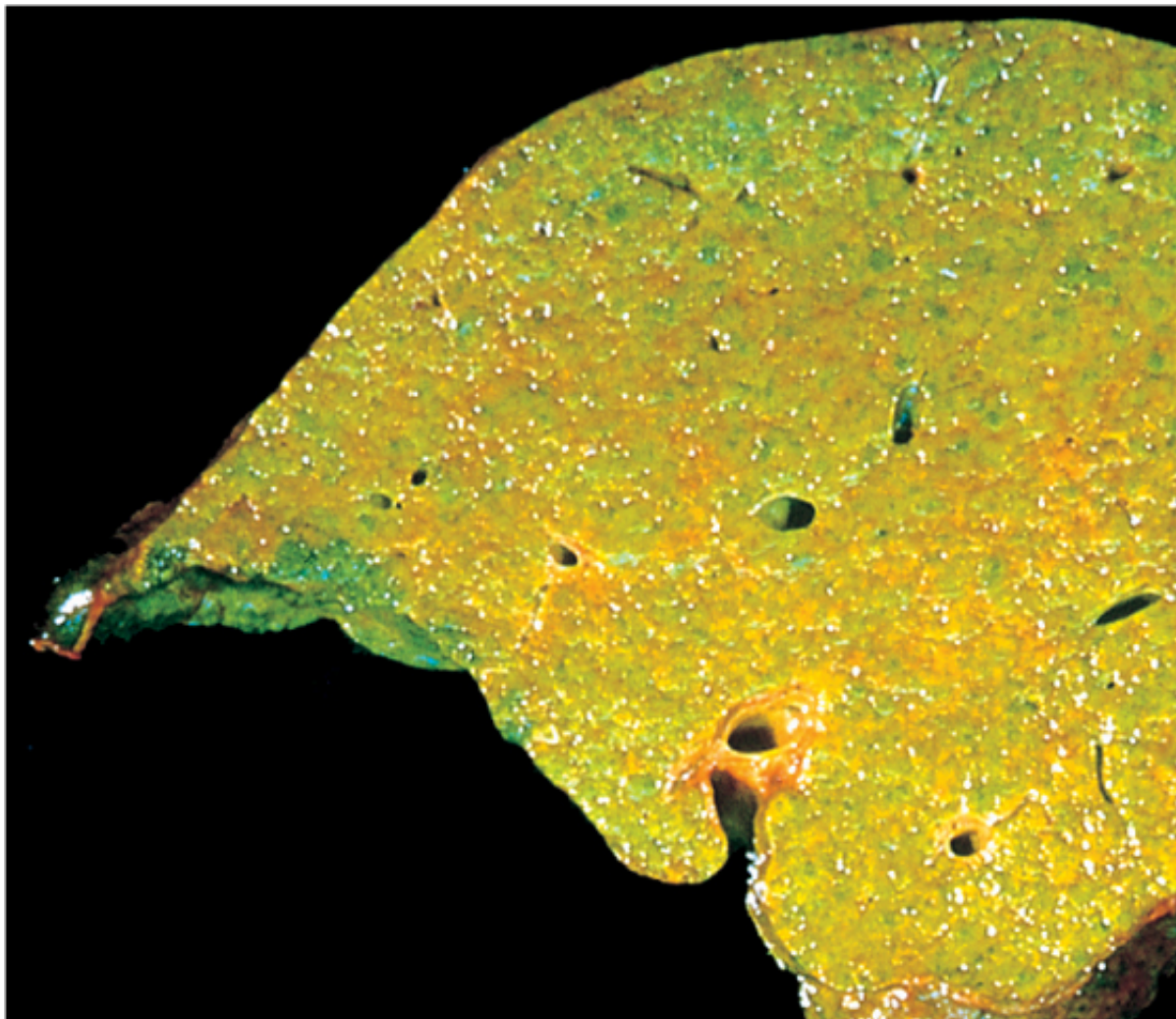
The onset of primary biliary cirrhosis is insidious, usually presenting as pruritus; jaundice develops over decades, the individuals develop hepatic decompensation, including portal hypertension with variceal bleeding and encephalopathy. *Serum alkaline phosphatase and cholesterol levels are almost always elevated; and usually signifies incipient hepatic decompensation.* Associated extrahepatic conditions include Sjögren syndrome, scleroderma, thyroiditis, rheumatoid arthritis, Raynaud phenomenon, celiac disease.

### Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic cholestatic disorder, characterized by progressive fibrosis of the large intrahepatic bile ducts. Because the changes in the ducts are patchy, retrograde cholangiography shows the contrast medium in the affected segments of the biliary tree. The large bile ducts show periductal fibrosis, leaving a solid cord scar with few inflammatory cells. Primary sclerosing cholangitis is commonly associated with inflammatory bowel disease (Chapter 15), particularly chronic ulcerative colitis, which coexists in approximately 80% of patients. The prevalence of primary sclerosing cholangitis in persons with ulcerative colitis is about 4%. The disease usually begins in the fifth decades, most often after development of inflammatory bowel disease. Males are affected more frequently than females.

#### *Pathogenesis and Clinical Course*

The cause of primary sclerosing cholangitis is unknown. The association with ulcerative colitis, the presence of antinuclear cytoplasmic antibodies with a perinuclear localization (Chapter 10) in 80% of patients, and the presence of antimitochondrial antibodies in a minority of patients suggest an immunologically mediated disease. Asymptomatic patients may come to attention only on the basis of an elevated serum alkaline phosphatase. Severely afflicted persons show symptoms associated with chronic liver disease, including fatigue, pruritus, and jaundice. Primary sclerosing cholangitis generally has a poor prognosis. Cholangiocarcinoma may develop in 10% to 15% of individuals with primary sclerosing cholangitis. There is no effective therapy for primary sclerosing cholangitis, and the disease has been treated by liver transplantation.



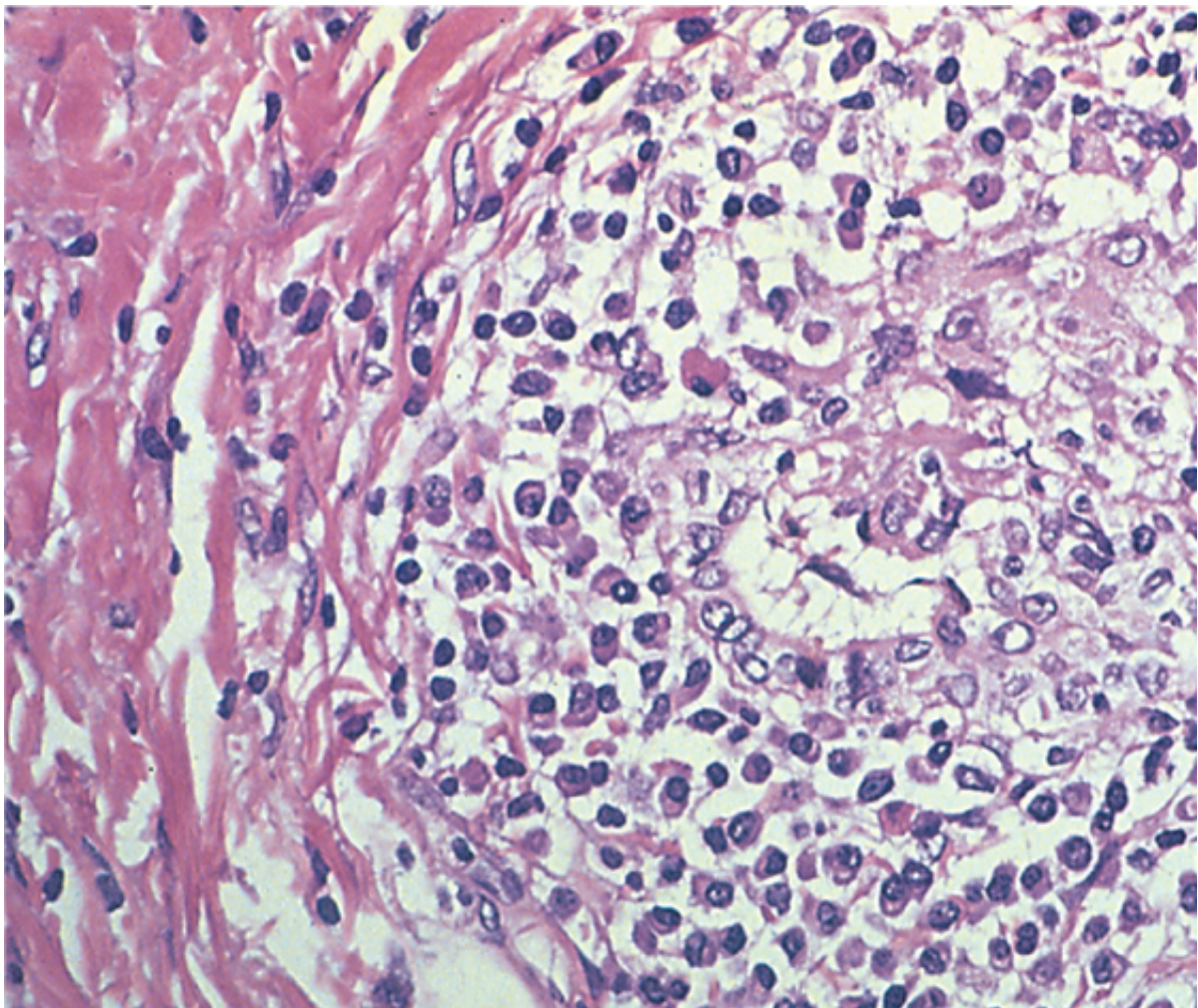
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Figure 16-23 Primary biliary cirrhosis. This sagittal section through the liver demonstrates the fine nodularity and b



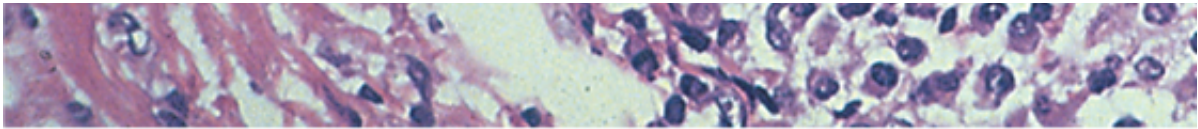
## Morphology

In all primary biliary cirrhosis and primary sclerosing cholangitis, the end-stage live yellow-green pigmentation, associated with marked icteric discoloration of body tissue surface, the liver is hard, with a finely granular appearance ([Fig. 16-23](#)). Interlobular bile ducts are destroyed by inflammation (the end stage of **primary biliary cirrhosis**). However, the morphology of this disease resembles the precirrhotic stage. Interlobular bile ducts are destroyed by inflammation (the **floppy** intraepithelial infiltration of lymphocytes and accompanying granulomatous inflammation). The portal tract infiltrate of lymphocytes, macrophages, plasma cells, and occasional eosinophils. The obstruction to intrahepatic bile flow leads to upstream bile ductular proliferation and inflammation and necrosis of the adjacent periportal hepatic parenchyma, and generally over years to decades, relentless portal tract scarring and bridging fibrosis leads to cirrhosis.

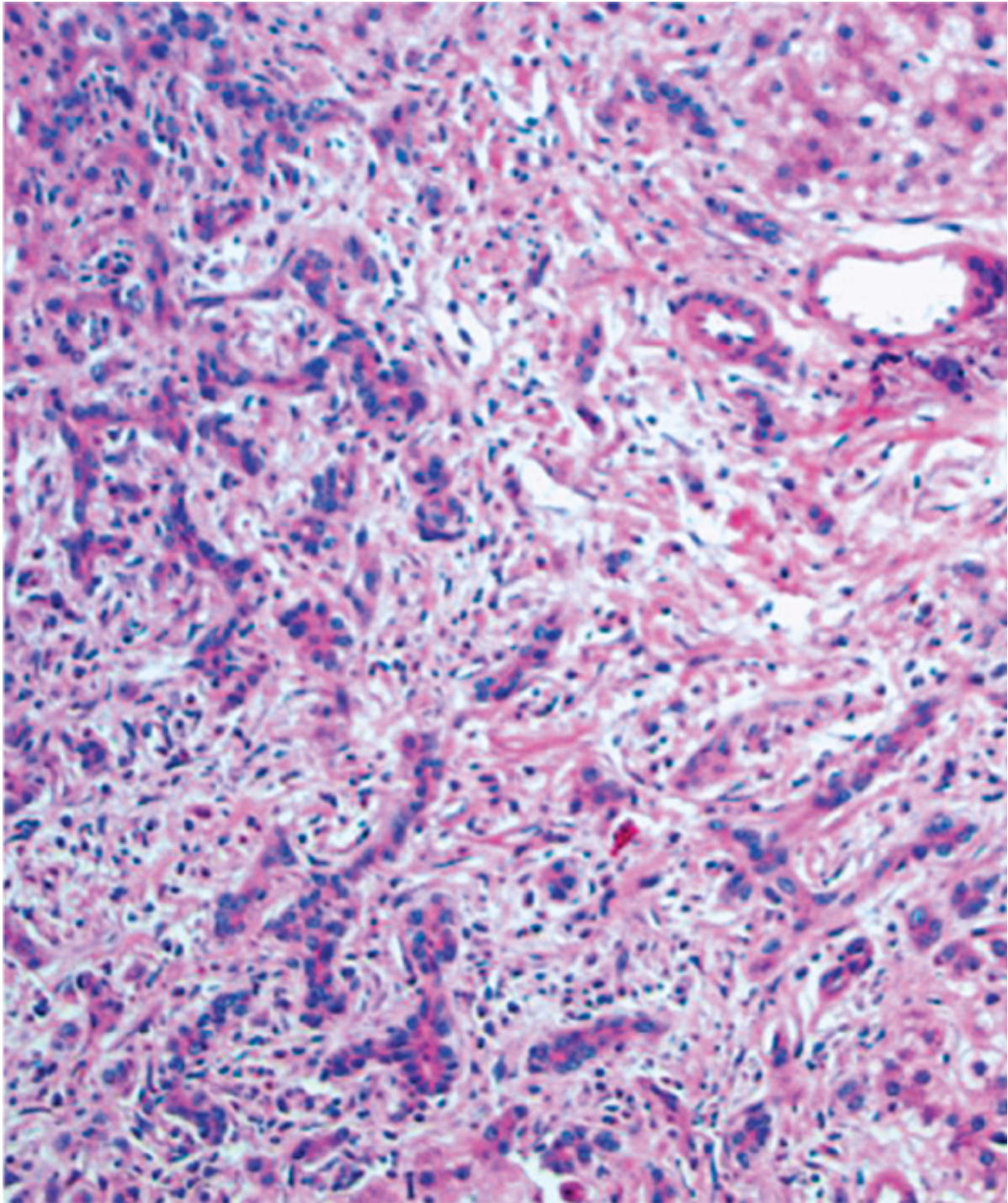
The characteristic feature of **primary sclerosing cholangitis** is a fibrosing cholangitis. Specifically, affected portal tracts show concentric periductal onion-skin fibrosis and an infiltrate (Fig. 16-26). Progressive atrophy of the bile duct epithelium leads to obliteration, leaving behind a solid, cordlike fibrous scar. In between areas of progressive strictures and ectatic and inflamed, presumably the result of down-stream obstruction. As the disease progresses over years, the entire liver becomes markedly cholestatic and fibrotic. Ultimately, biliary cirrhosis like that seen with primary and secondary biliary cirrhosis.







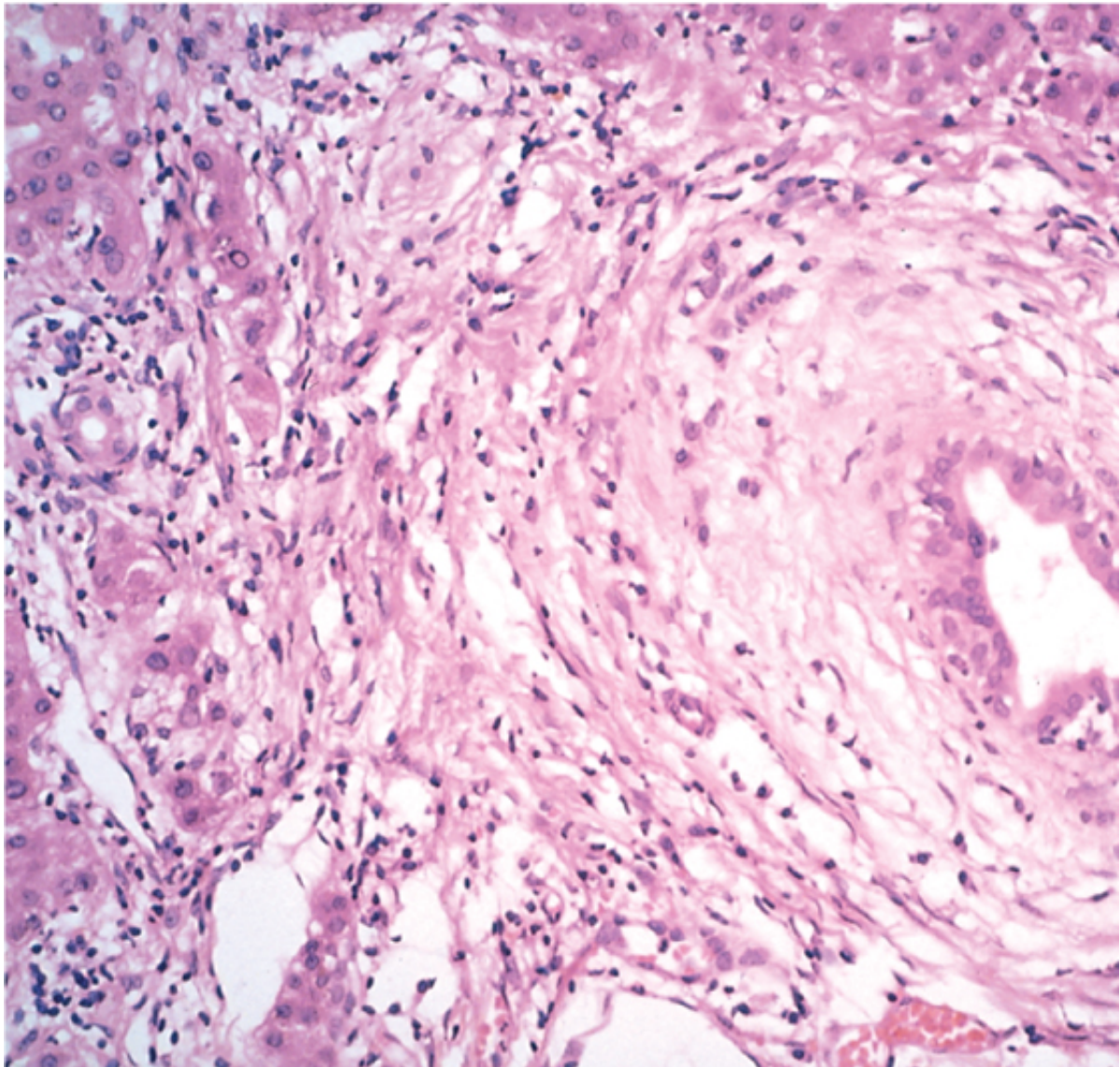
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 Figure 16-24 Primary biliary cirrhosis. A portal tract is markedly expanded by an infiltrate of lymphocytes and plasma cells, with a bile duct undergoing destruction (florid duct lesion).



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 Figure 16-25 An example of ductular proliferation in a fibrotic septum. (Courtesy of Dr. Matthew Yeh, University of California, San Francisco)



Figure 16-26 An example of ductular proliferation in a fibrotic septum. (Courtesy of Dr. Matthew Ten, University of Michigan)



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Figure 16-26 Primary sclerosing cholangitis. A bile duct undergoing degeneration is entrapped in a dense band of fibrous connective tissue.



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## CIRCULATORY DISORDERS

Given the enormous flow of blood through the liver, it is not surprising that circulatory disturbances occur. These disorders can be grouped according to whether blood flow into, through, or from the liver is

### Impaired Blood Flow into the Liver

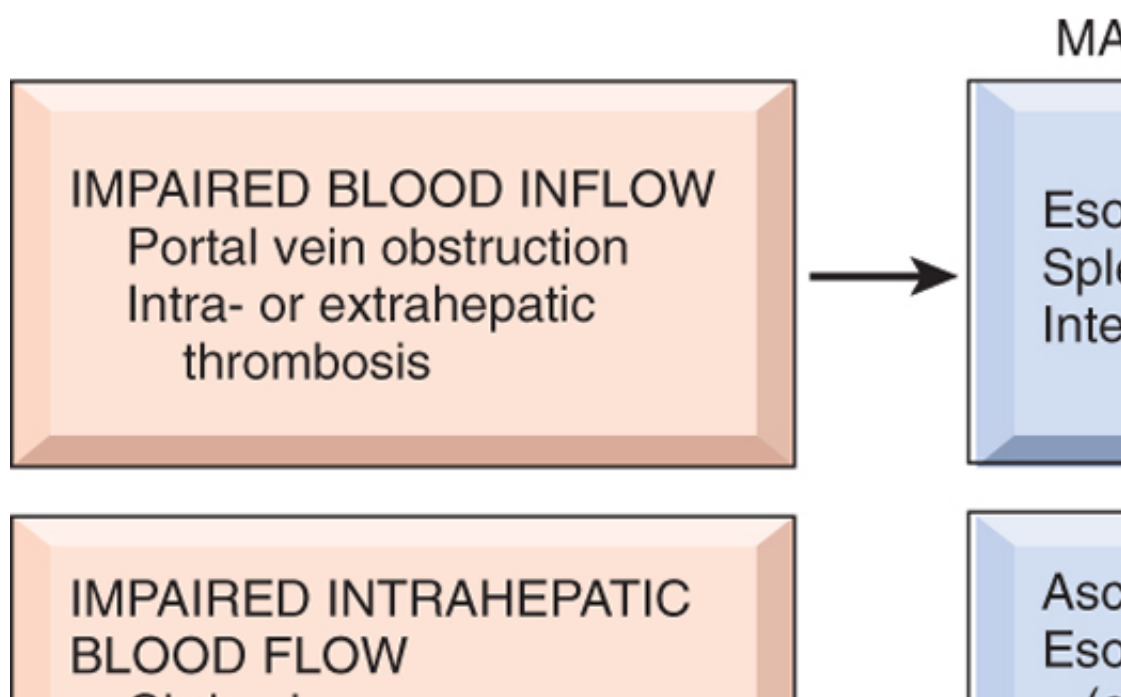
#### *Hepatic Artery Inflow*

*Liver infarcts* are rare, thanks to the double blood supply to the liver. Interruption of the main hepatic artery results in ischemic necrosis of the organ, because retrograde arterial flow through accessory vessels and the portal vein can maintain some blood flow through the liver parenchyma. The one exception is hepatic artery thrombosis in the transplanted liver, which is almost always fatal. Thrombosis or compression of an intrahepatic branch of the hepatic artery by polyarteritis nodosa or tumor invasion may result in a localized parenchymal infarct.

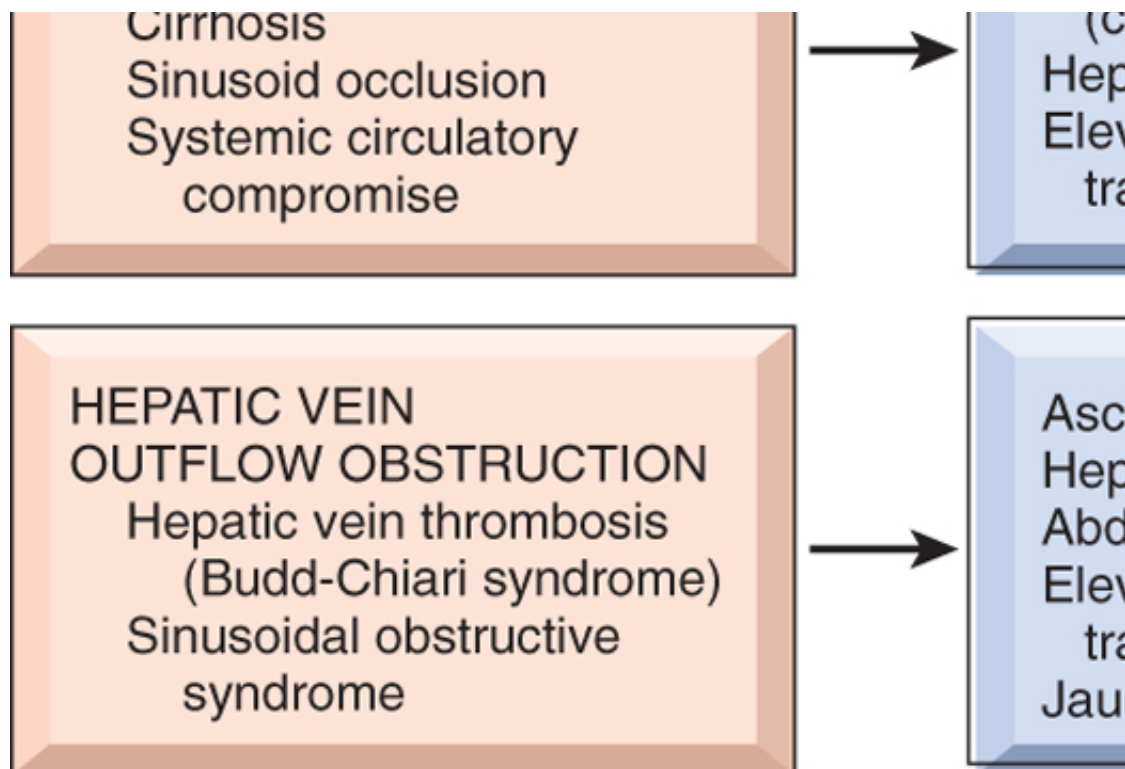
#### *Portal Vein Obstruction and Thrombosis*

Blockage of the portal vein may be insidious and well tolerated or may be a catastrophic and potentially fatal event. Occlusion of the portal vein or its major branches typically produces abdominal distention, ascites and other manifestations of portal hypertension, principally esophageal varices that are prone to bleed. Chronic liver disease, if present, is often massive and intractable. Acute impairment of visceral blood flow leads to profound shock. Extrahepatic portal vein obstruction may arise from the following:

Peritoneal sepsis (e.g., acute diverticulitis or appendicitis leading to pylephlebitis in the spleen) initiates splenic vein thrombosis, which propagates into the portal vein. Thrombogenic diseases such as myeloproliferative disorders, thromboses. Vascular invasion by primary or secondary cancer in the liver that progressively involves the portal vein. Extensions of hepatocellular carcinoma can even occlude the main portal vein. Banti syndrome, a rare condition, is portal vein (as from neonatal omphalitis or umbilical vein catheterization) produces a fibrotic obliteration of the portal vein presenting as splenomegaly or esophageal varices years after the occlusive event.







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Figure 16-27 Hepatic circulatory disorders. The forms and clinical manifestations of compromise

Intrahepatic thrombosis of a portal vein radicle, when acute, does not cause ischemic infarction but a small area of red-blue discoloration (so-called *infarct of Zahn*). There is no necrosis, only hepatocellular distended sinusoids. *Hepatoportal sclerosis* is a chronic, generally bland condition of progressive portal vein inflow. In those instances in which a cause can be identified, it may be a myeloproliferative disorder, hypercoagulability, peritonitis, or exposure to arsenicals.

### Impaired Blood Flow through the Liver

The most common intrahepatic cause of portal blood flow obstruction is cirrhosis, as was described above. In sickle cell disease, the hepatic sinusoids are occluded by sickle cells, and the resulting congestion and necrosis of the sinusoids occurs in a small but important group of diseases. In sickle cell disease, the hepatic sinusoids are occluded by sickle cells, and the resulting congestion and necrosis of the sinusoids occurs in a small but important group of diseases. In sickle cell disease, the hepatic sinusoids are occluded by sickle cells, and the resulting congestion and necrosis of the sinusoids occurs in a small but important group of diseases.

### Passive Congestion and Centrilobular Necrosis

These hepatic manifestations of systemic circulatory disorders constitute a morphologic continuum. Passive congestion of the liver, and if persistent, can cause centrilobular necrosis, and peripheral necrosis. In most instances, the only clinical evidence of centrilobular necrosis is a small elevation of serum aspartate aminotransferase. In most instances, the only clinical evidence of centrilobular necrosis is a small elevation of serum aspartate aminotransferase.

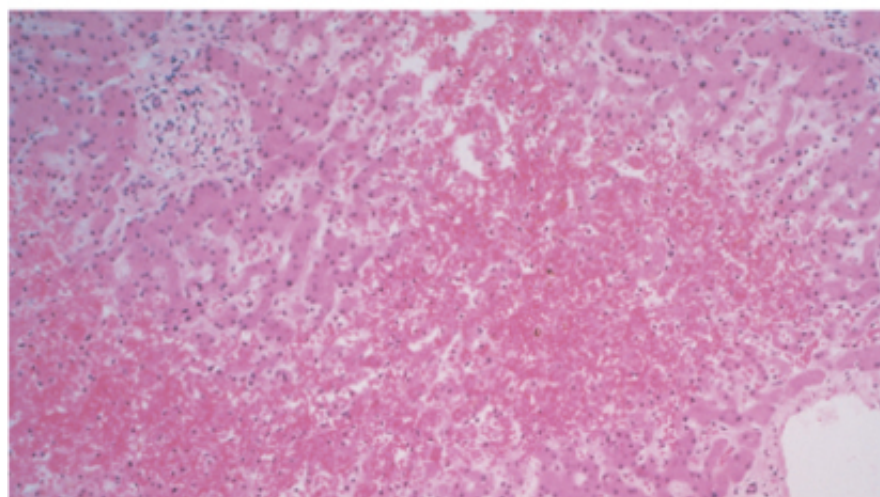
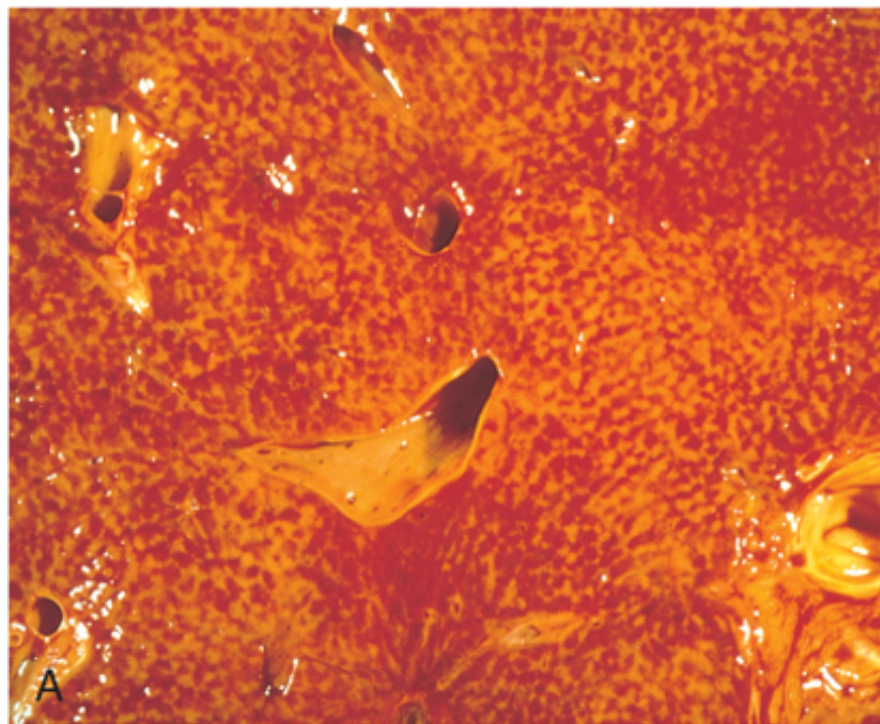
#### Morphology

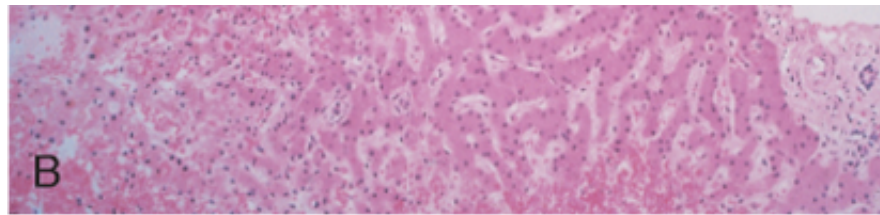
In right-sided cardiac failure, the liver is slightly enlarged, tense, and cyanotic, with a bluish discoloration. Microscopically, there is congestion of centrilobular sinusoids. With time, centrilobular necrosis occurs, resulting in markedly attenuated liver cell cords. An uncommon complication of severe congestive heart failure is so-called cardiac sclerosis. The pattern of liver fibrosis is inasmuch as it is mostly centrilobular. The damage rarely fulfills the accepted criteria for cirrhosis, but the historically sanctified term *cardiac cirrhosis* cannot easily be dislodged.

Left-sided cardiac failure or shock may lead to hepatic hypoperfusion and hypoxia. hepatocytes in the central region of the lobule undergo ischemic necrosis. There is viable hepatocytes in the periportal region versus necrotic hepatocytes in the central parenchyma. The combination of left-sided hypoperfusion and right-sided retrograde synergistically to generate a distinctive lesion, centrilobular hemorrhagic necrosis ( on a variegated mottled appearance, reflecting hemorrhage and necrosis in the center alternating with pale midzonal areas, known traditionally as the **"nutmeg" liver**.

### ***Peliosis Hepatis***

Sinusoidal dilation occurs in any condition in which efflux of hepatic blood is impeded. Peliosis hepatis is primary. It is most commonly associated with exposure to anabolic steroids and, rarely, pathogenesis is not known. Although clinical signs are generally absent even in advanced peliosis hemorrhage or hepatic failure may occur. Peliotic lesions usually disappear after cessation of drug





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 Figure 16-28 Centrilobular hemorrhagic necrosis (nutmeg liver). **A**, The cut liver section, in which major blood vessels are visible, giving the liver a red appearance, representing hemorrhage in the centrilobular regions of the parenchyma. **B**, Microscopically, the architecture is lost, and hepatocytes are not readily visible. Portal tracts and the periportal parenchyma are relatively spared.

## Hepatic Vein Outflow Obstruction

### **Hepatic Vein Thrombosis (Budd-Chiari Syndrome)**

The Budd-Chiari syndrome results from the thrombosis of two or more major hepatic veins and is associated with ascites, and abdominal pain. Hepatic vein thrombosis is associated with (in order of frequency): polycythemia vera, pregnancy, the postpartum state, the use of oral contraceptives, paroxysmal nocturnal hemoglobinuria, abdominal cancers, particularly hepatocellular carcinoma. All these conditions produce thrombotic tendencies, sluggish blood flow. Some cases are caused by mechanical obstruction to blood outflow by a parasitic cyst, or by obstruction of the inferior vena cava at the level of the hepatic veins by thrombosis.

#### **Morphology**

With acutely developing thrombosis of the major hepatic veins or inferior vena cava, the liver is enlarged, red-purple, and has a tense capsule (Fig. 16-29). Microscopically, the affected hepatic lobules show severe centrilobular congestion and necrosis. Centrilobular fibrosis develops in late stages. In chronic thrombosis is more slowly developing. The major veins may contain totally occlusive thrombi, or, in chronic cases, organized adherent thrombi.

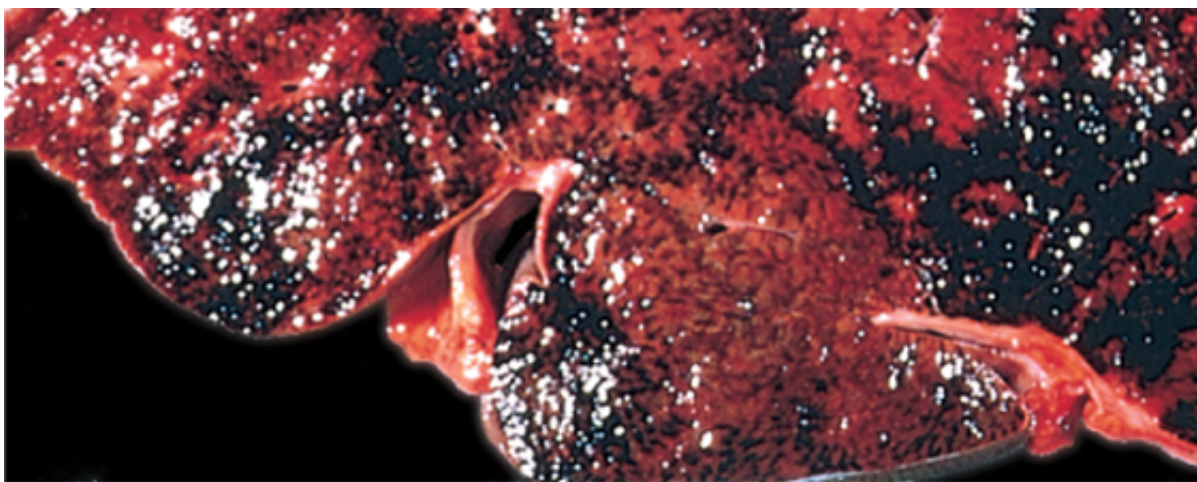
The mortality from untreated acute Budd-Chiari syndrome is high. Prompt surgical creation of a portocaval anastomosis to reverse flow through the portal vein and improves the prognosis considerably; direct dilation of the inferior vena cava by angiography. The chronic form of the syndrome is far less grave, and more than two-thirds of the

### **Sinusoidal Obstruction Syndrome**

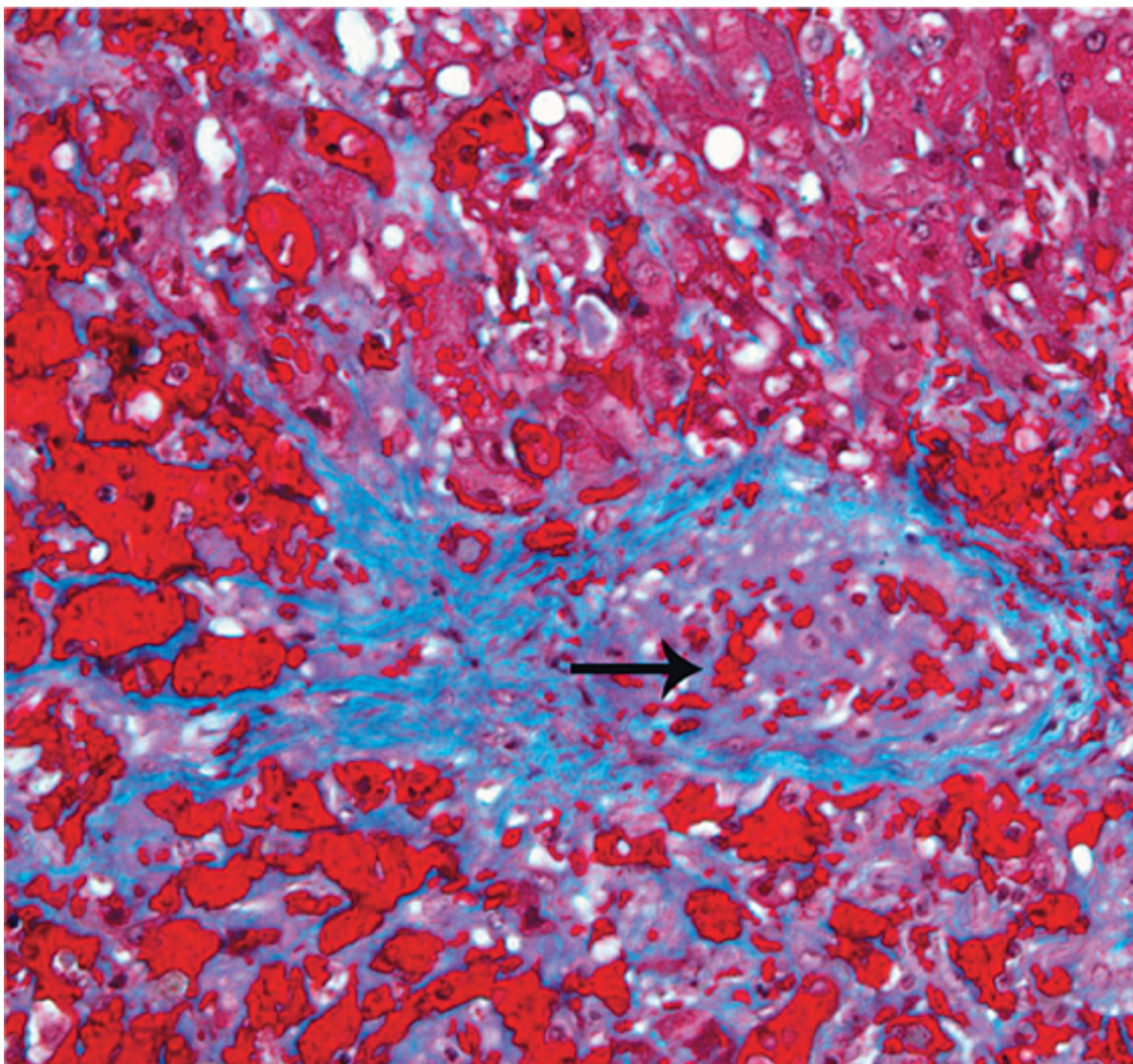
Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloid, this condition is now known as sinusoidal obstruction syndrome. The new name indicates that sinusoidal obstruction syndrome is caused by toxic injury to sinusoidal endothelial cells which slough off and create emboli that block blood flow. Endothelial damage is accompanied by peliosis hepatis, proliferation of stellate cells, and fibrosis of terminal branches of the hepatic vein (Fig. 16-30). The syndrome occurs primarily in the first 20-30 days after bone marrow transplantation. The sinusoidal injury is caused by cyclophosphamide<sup>®</sup>, and by total body radiation, used in pre- or post-transplantation regimens. Transplant recipients of allogeneic marrow transplants. The presentation of the disease varies from mild to severe. The syndrome that does not resolve after 3 months of treatment can cause death.



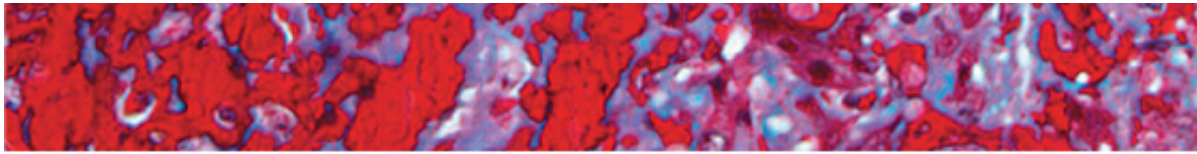




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 Figure 16-29 Budd-Chiari syndrome. Thrombosis of the major hepatic veins has caused extren







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 Figure 16-30 Sinusoidal obstruction syndrome (formerly known as veno-occlusive disease). A central vein is occluded by fibrous tissue. There is also fibrosis in the sinusoidal spaces. Fibrous tissue is stained *blue* by the Masson trichrome stain. (Kumar et al, Robbins Basic Pathology, 8e, Elsevier, Philadelphia, Pennsylvania, 2007.)

## SUMMARY

### Circulatory Disorders

Circulatory disorders of the liver can be caused by impaired blood inflow, decreased blood flow, and obstruction of blood outflow. Portal vein obstruction by intra or extrahepatic causes cause portal hypertension, esophageal varices, and ascites. The most common intrahepatic blood flow is cirrhosis. Obstructions of blood outflow include hepatic vein obstruction (Budd-Chiari syndrome) and sinusoidal obstruction syndrome, previously known as veno-occlusive disease.



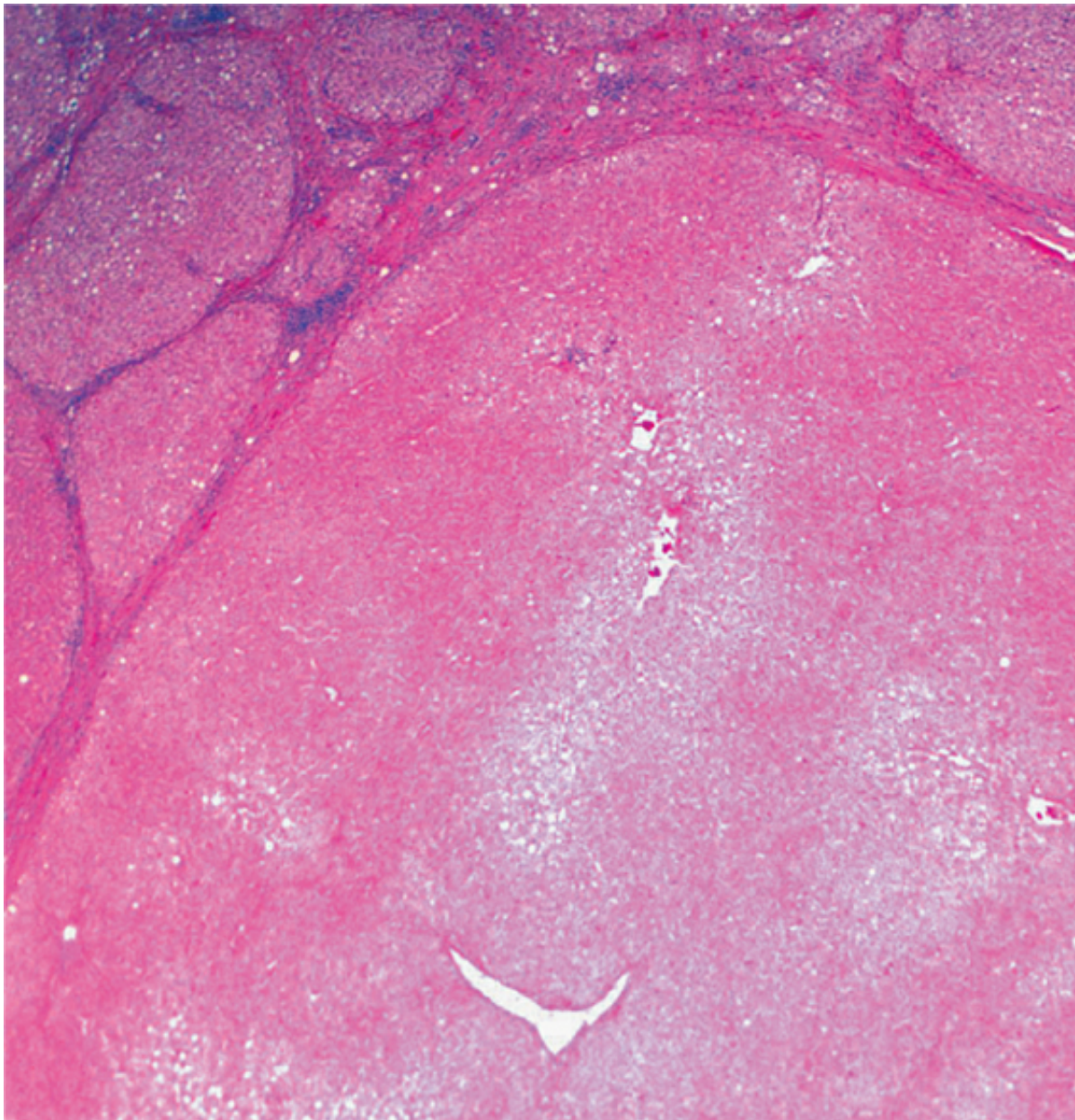
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## TUMORS AND HEPATIC NODULES

The liver and lungs share the dubious distinction of being the visceral organs most often involved. Indeed, *the most common hepatic neoplasms are metastatic carcinomas*, with colon, lung, and breast as the primary tumor. The incidence of *primary hepatic malignancies*, almost entirely constituted by *hepatocellular carcinoma*, varies widely throughout the world, as discussed later. Two rare types of primary liver tumors are not discussed further: *hepatoma*, and *angiosarcoma*, a tumor of blood vessels that is associated with exposure to vinylchloride. They may generate epigastric fullness and discomfort or be detected only on radiographic studies for other indications may pick up incidental liver masses. Here we discuss primary tumors of the liver.

### Hepatocellular Nodules



Solitary or multiple benign hepatocellular nodules may develop in the liver. These include lesions macroregenerative nodules, and dysplastic nodules.

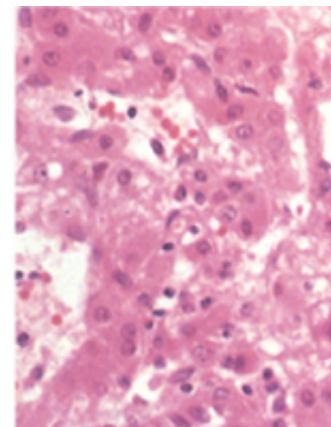
*Focal nodular hyperplasia* is a localized, well-demarcated but poorly encapsulated lesion, c nodules with a central fibrous scar. The nodules appear in noncirrhotic livers and may reac Focal nodular hyperplasia, as the name indicates, is not a neoplasm but a nodular regener vascular injury. It is usually an incidental finding, most commonly in women of reproductive malignancy. In about 20% of cases, focal nodular hyperplasia coexists with hepatic cavern below). *Macroregenerative* nodules appear in cirrhotic livers (Fig. 16-31). They are larger th not display atypical features. Macroregenerative nodules contain more than one portal trac do not seem to be precursors of malignant lesions. *Dysplastic nodules* are lesions larger th cirrhotic livers. Hepatocytes in dysplastic nodules and in smaller lesions called dysplastic fo atypical features such as crowding and pleomorphism. The dysplastic features can be of lo lesions are considered to be precursors of hepatocellular cancers, are often monoclonal, a similar to those present in liver cancers. Dysplastic lesions are subdivided into small-cell a Only small-cell dysplasias are precursors to cancer; large-cell dysplastic lesions contain he replicative senescence.

## Benign Tumors

The most common benign lesions of the liver are *cavernous hemangiomas*, which are identical to (Chapter 10). These well-circumscribed lesions consist of endothelial cell-lined vascular channels discrete red-blue, soft nodules, usually less than 2 cm in diameter, often directly beneath the caps importance of not mistaking them for metastatic tumors; blind percutaneous needle biopsy may ca

### Hepatic Adenoma

This benign neoplasm of hepatocytes usually occurs in women of childbearing age who have use regress on discontinuance of hormone use. These tumors may be pale, yellow-tan or bile-stained anywhere in the hepatic substance but often beneath the capsule (Fig. 16-32). They may reach 3l adenomas are composed of sheets and cords of cells that may resemble normal hepatocytes or l size. Portal tracts are absent; instead, prominent arterial vessels and draining veins are distributer Liver cell adenomas are significant for three reasons: (1) when they present as an intrahepatic ma ominous hepatocellular carcinoma; (2) subcapsular adenomas are at risk for rupture, particularly c stimulation), causing life-threatening intra-abdominal hemorrhage; and (3) although adenomas are hepatocellular carcinoma, adenomas carrying  $\beta$ -catenin mutations carry a risk of developing into c







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Figure 16-32 Hepatic adenoma. **A**, Surgically resected specimen showing a discrete mass underneath the liver capsule with cords of hepatocytes.

## Hepatocellular Carcinomas (HCC)

### *Epidemiology*

Worldwide, HCC (also known as liver cell carcinoma or, erroneously, hepatoma) constitutes approximately 1% of all cancer deaths. Incidence varies widely in different areas of the world. More than 85% of cases occur in countries where HBV is transmitted vertically, and, as already discussed, the carrier state starts in infancy. Moreover, exposure to aflatoxin, which, combined with HBV infection, increases the risk of HCC development in nonexposed populations. The peak incidence of HCC in these areas is between 20 and 40 years of age and may appear in the absence of cirrhosis. In Western countries HCC incidence is rapidly increasing in the last 25 years, but it is still much lower (8- to 30-fold) than the incidence in some Asian countries. It is present before age 60, and in almost 90% of cases tumors develop in persons with cirrhosis.

There is a pronounced male preponderance of HCC throughout the world, about 3 : 1 in low-incidence areas. These differences may be related to the greater prevalence of HBV infection, alcohol consumption, and in males.

### *Pathogenesis*

Several general factors relevant to the pathogenesis of HCC were discussed in Chapter 6. Only a brief review is given here.

Three major etiologic associations have been established: infection with HBV or HCV, chronic alcoholism, and hemochromatosis. Other conditions include hemochromatosis and tyrosinemia. Many variables, including age, sex, alcohol, and nutrition, interact in the development of HCC. For example, the disease most commonly associated with hemochromatosis, in which almost 40% of patients develop this tumor, the development of cirrhosis seems to be an important, but not requisite, contributor to the emergence of HCC. In the presence of cell injury and replication, as occurs in chronic viral hepatitis, the risk of HCC is greatly enhanced. In Japan and Central Europe, chronic HCV infection is the greatest risk factor in the development of HCC. In patients with hepatitis C occurs almost exclusively in the setting of cirrhosis. In certain regions of Africa, where HBV is endemic, there is also high exposure to dietary aflatoxins derived from *Aspergillus* fungi. Carcinogenic toxins are found in "moldy" grains and peanuts. Aflatoxin can bind covalently to DNA and protein, and is a potent carcinogen.



Despite the detailed knowledge about the etiologic agents of HCC, the pathogenesis of the tumor *develops from small-cell, high-grade dysplastic nodules in cirrhotic livers*. As already discussed, they may contain chromosomal aberrations similar to those seen in HCCs. The cell of origin of HCC has been a matter of debate. It seems that *the tumors may arise from both mature hepatocytes and progenitor cells (Kupfer cells)*. Distinguishing high-grade dysplastic nodules from early HCC is difficult even in biopsies, because of the overlap of features for these stages. An important criterion is nodule vascularization, visualized by imaging, which is a criterion for malignancy.

*An almost universal feature of HCC is the presence of structural and numeric chromosomal abnormalities.* Genetic instability is not known, but some entities seem to be most important:

Cell death, hepatocyte replication, and inflammation, seen in all forms of chronic hepatitis, can lead to DNA damage. Poor regulation of hepatocyte replication can occur by point mutations or overexpression of growth factors (such as  $\beta$ -catenin), mutations or loss of heterozygosity of tumor suppressor genes (such as p53), or constitutive expression of growth factors. Defects in DNA repair, particularly those in repair of double-strand breaks, perpetuate DNA damage and may cause chromosome defects.

Neither HBV nor HCV contains oncogenes. The already mentioned *HBV-X* gene may have some tumorigenic capacity of these viruses probably relates primarily to their capacity to cause continuous liver regeneration.

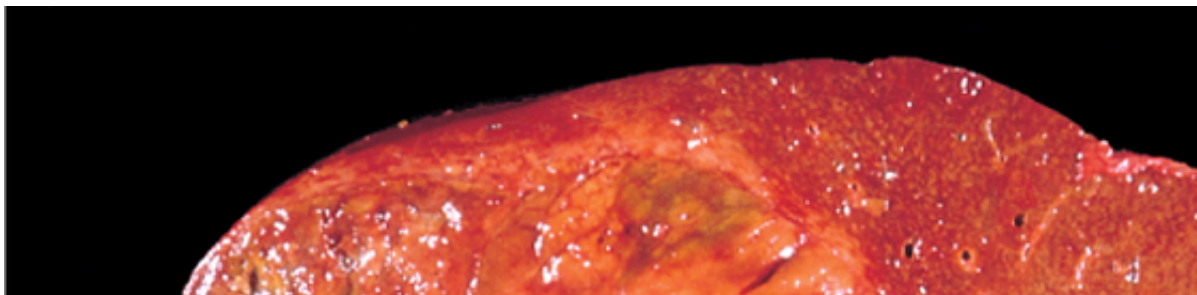
### Morphology

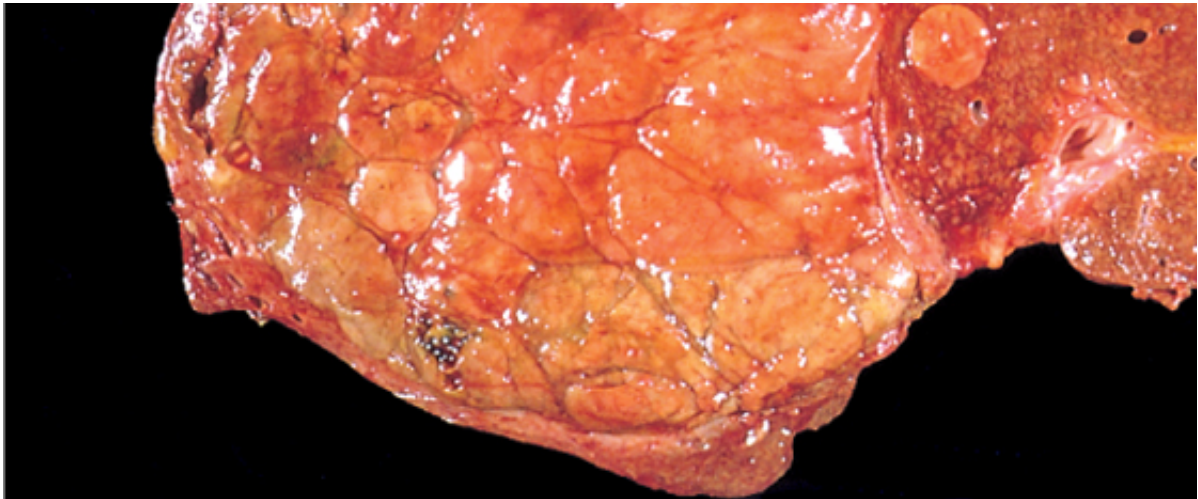
Primary liver carcinomas, of which almost all are HCC, may appear grossly as (1) a massive tumor (Fig. 16-33); (2) a **multifocal tumor** made of nodules of variable size; (3) an **infiltrative** cancer, permeating widely and sometimes involving the entire liver, like the cirrhotic liver background. Particularly in the latter two patterns, it may be difficult to distinguish regenerative nodules of cirrhotic liver from nodules of neoplasm of similar size. Dissecting the tumor usually reveals yellow-white, punctuated sometimes by bile staining and areas of hemorrhage. **Patterns of HCC have a strong propensity for invasion of vascular channels.** Hematogenous metastases ensue, and occasionally snakelike masses of tumor invade the portal vein (portal circulation) or inferior vena cava, extending even into the right side of the heart.

Histologically, HCCs range from well-differentiated lesions that reproduce hepatocyte trabeculae or glandular patterns (Fig. 16-34), to poorly differentiated lesions, often composed of multinucleate anaplastic tumor giant cells. **In the better differentiated variants, glycogen is found within the cytoplasm of cells and in pseudocanaliculi between cells.** Acidophilic granules within the cytoplasm may be present, resembling Mallory bodies. There is surprising variability in HCCs, explaining the soft consistency of these tumors.

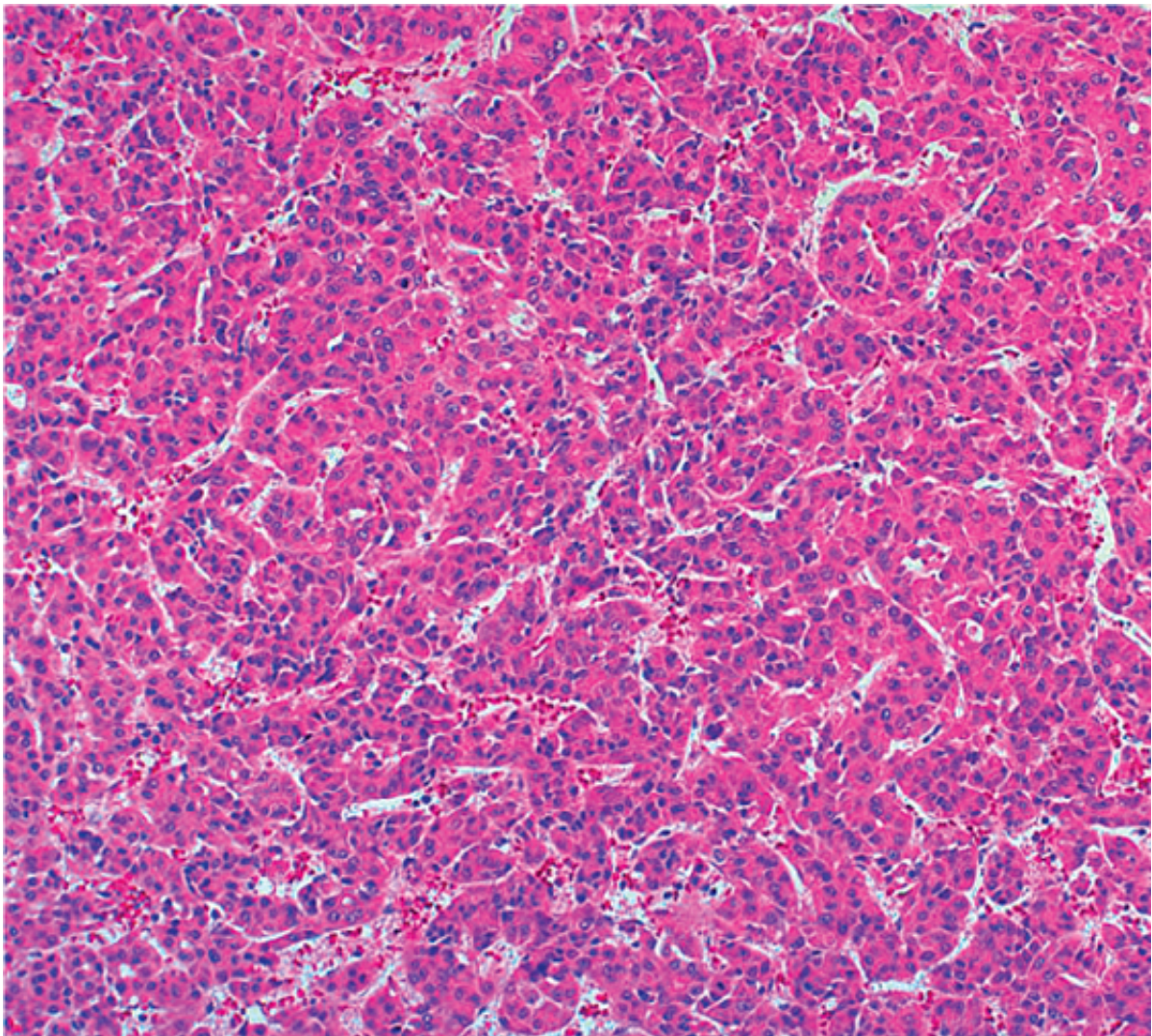
A distinctive clinicopathologic variant of HCC is the **fibrolamellar carcinoma**, which occurs in children and young adults (20-40 years of age) with equal incidence, has no association with cirrhosis or viral factors (Fig. 16-35). It usually consists of a single large, hard "scirrhous" tumor with a firm consistency, through which, vaguely resembling focal nodular hyperplasia. Histologically it is composed of polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagenous connective tissue.

### Clinical Features





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 Figure 16-33 Hepatocellular carcinoma, unifocal, massive type. A large neoplasm with extensive areas of necrosis in noncirrhotic liver. A satellite tumor nodule is directly adjacent.



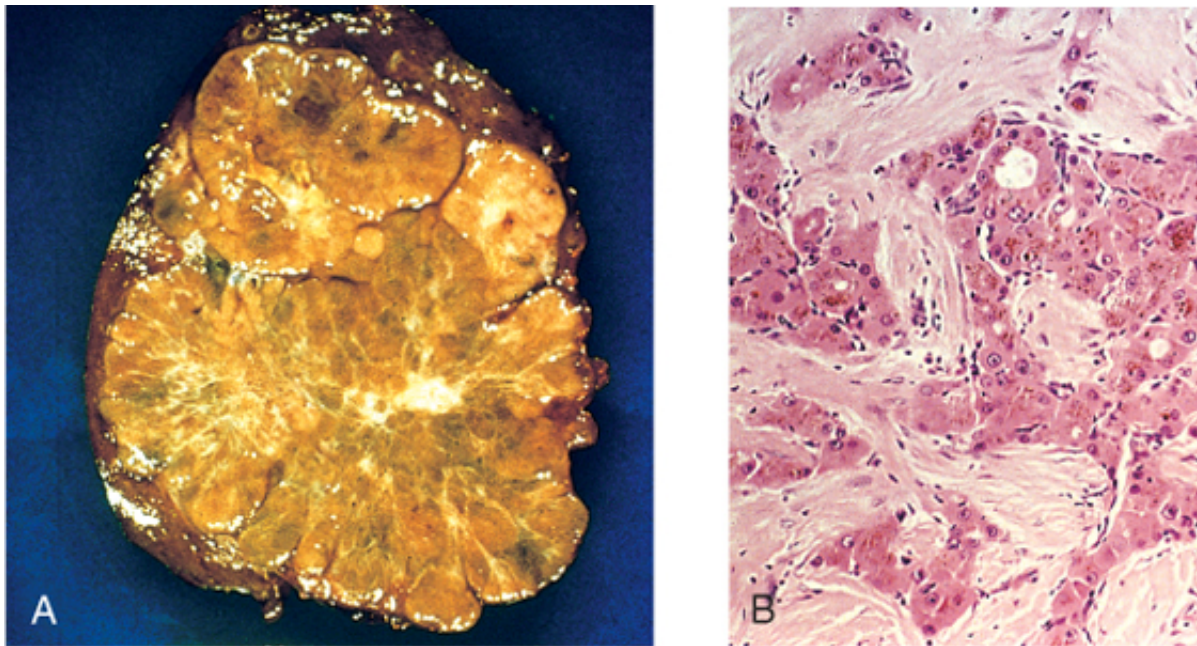




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Figure 16-34 Hepatocellular carcinoma Carcinoma cells forming trabecular, pseudoacinar, and pseudoglandular patterns (H&E stain, University of Washington, Seattle, Washington.)

Although primary carcinomas in the liver may present with silent hepatomegaly, they are often encountered in patients who already have symptoms of the underlying disorder. In these persons, *rapid increase in the size of the liver, the appearance of bloody ascites, fever, and pain call attention to the development of a tumor.* These symptoms are diagnostic. Approximately 50% of patients have elevated serum  $\alpha$ -fetoprotein. However, this tumor can also cause modest elevations are also encountered in other conditions, such as cirrhosis, massive liver necrosis, and fetal distress or death, fetal neural tube defects such as anencephaly and spina bifida (Chapter 23: 18). *Very high levels (>1000 ng/mL), however, are rarely encountered except in HCC.*



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Figure 16-35 Fibrolamellar carcinoma. **A**, Resected specimen with an outer rim of normal liver. **B**, Nests of tumor cells separated by bands of collagenous connective tissue.

The overall prognosis of HCC is grim, but it is significantly better for individuals who have a single tumor and good liver function. The median survival is 7 months, with death from (1) profound cachexia, (2) gastrointestinal bleeding, (3) liver failure with hepatic coma, or (4) rarely, rupture of the tumor with fatal hemorrhage. The most effective therapies are surgical resection of smaller tumors and liver transplantation for patients with small tumors and good liver function. The recurrence rate is greater than 60% at 5 years. The best hope for preventing HCC in regions endemic for HBV is an anti-HBV immunization program.

## SUMMARY

### Liver Tumors

The liver is the most common site of metastatic cancers from primary tumors of the gastrointestinal tract. The main primary tumors are hepatocellular carcinomas and cholangiocarcinomas. Hepatocellular carcinomas are by far the most common. HCC is a common tumor in Asia and Africa, and its incidence is increasing in the United States. The main etiologic factors for hepatocellular carcinoma are hepatitis B and C, alcoholic cirrhosis, hemochromatosis, and rarely, tyrosinemia. In the Western population about 90% of hepatocellular carcinomas develop in cirrhotic livers; in Asia almost 50% of cases develop in noncirrhotic livers. The

and cellular regeneration associated with viral hepatitis may be predisposing to the development of carcinomas. Hepatocellular carcinomas may be unifocal or multifocal, and may involve blood vessels, and recapitulate normal liver architecture to varying degrees.



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## DISORDERS OF THE GALLBLADDER AND THE EXTRAHEPATIC BILIARY TRACT

Disorders of the gallbladder and biliary tract affect a large proportion of the world's population. *Cholelithiasis (gallstones)* accounts for more than 95% of these diseases. It is estimated that about 2% of the United States federal health budget is spent on cholelithiasis and its complications. Moreover, the burden of gallstones in the US population is calculated to weigh 25 to 50 tons, distributed among more than 20 million persons! In this section we first discuss gallbladder diseases (cholelithiasis and cholecystitis) and then examine some disorders of the extrahepatic bile ducts. It should be kept in mind that lesions of the extrahepatic biliary tract may extend to intrahepatic bile ducts and that tumors of the biliary tract (cholangiocarcinomas, described later) may have intra- or extrahepatic locations.





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## GALLBLADDER DISEASES

### **Cholelithiasis (Gallstones)**

Gallstones afflict 10% to 20% of adult populations in northern hemisphere Western countries. Adult American countries (20% to 40%) and are low in Asian countries (3% to 4%). In the United States gallstones diagnosed annually, and two-thirds of these individuals undergo surgery.

There are two main types of gallstones. *In the West about 80% are cholesterol stones, containing* remainder are composed predominantly of bilirubin calcium salts and are designated *pigment stones*.

#### *Pathogenesis and Risk Factors*

Bile is the only significant pathway for elimination of excess cholesterol from the body, either as free or as water insoluble and is rendered water soluble by aggregation with bile salts and lecithins secreted by the gallbladder. If concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain in solution and solid cholesterol monohydrate crystals form. Cholesterol gallstone formation involves four simultaneous processes:

Supersaturation of the bile with cholesterol  
Establishment of nucleation sites by microprecipitation  
Gallbladder stasis, which promotes nucleation  
Mucus hypersecretion to trap the crystals, encourage growth

The pathogenesis of pigment stones is also complex. It is clear, however, that the presence of underlying conditions increases the likelihood of pigment stone formation, as occurs in hemolytic anemias and infections. Gallstones are primarily insoluble calcium bilirubinate salts.

**Table 16-8. Risk Factors for Gallstones**

<b>Cholesterol Stones</b>
Demography: Northern Europeans, North and South Americans, Native Americans, Mexican Americans.
Advancing age
Female sex hormones
Female gender
Oral contraceptives
Pregnancy
Obesity
Rapid weight reduction
Gallbladder stasis
Inborn disorders of bile acid metabolism
Hyperlipidemia syndromes
<b>Pigment Stones</b>
Demography: Asian more than Western, rural more than urban
Chronic hemolytic syndromes
Biliary infection
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with

The major risk factors for gallstones are listed in [Table 16-8](#). However, 80% of individuals with gallstones are older than age 40 and female. Here we comment about some of these risk factors:

**Age and gender.** The prevalence of gallstones increases throughout life. In the United States, the prevalence is 10% to 20% in adults, and increases with age. In the United States, the prevalence is 10% to 20% in adults, and increases with age.

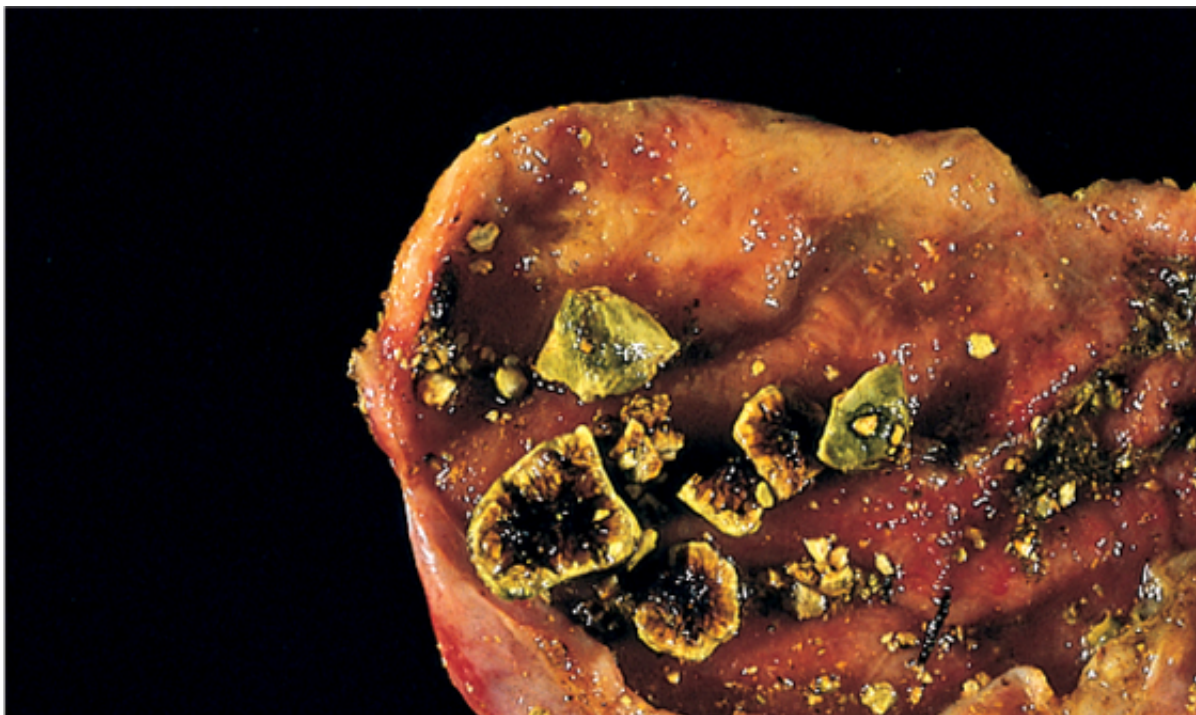
**Age and gender.** The prevalence of gallstones increases throughout life. In the United States, 10% of those younger than age 40 have stones, in contrast to 25% to 30% of those older than 80 years. The prevalence is twice as high in women as in men. **Ethnic and geographic.** Cholesterol gallstone prevalence approaches 100% in the Pima, Hopi, and Navajos—whereas pigment stones are rare; the prevalence seems to be related to hypersecretion. Gallstones are more prevalent in Western industrialized societies and uncommon in those of the Third World. In addition to ethnicity, family history alone imparts increased risk, as do a variety of inborn errors associated with impaired bile salt synthesis and secretion. **Environment.** Estrogenic influence, pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion, weight loss, and treatment with the hypocholesterolemic agent **clofibrate**<sup>®</sup> are also strongly associated with cholesterol secretion. **Acquired disorders.** Any condition in which gallbladder motility is reduced, such as pregnancy, rapid weight loss, and spinal cord injury. In most cases, however, gallbladder hypomotility is the cause.

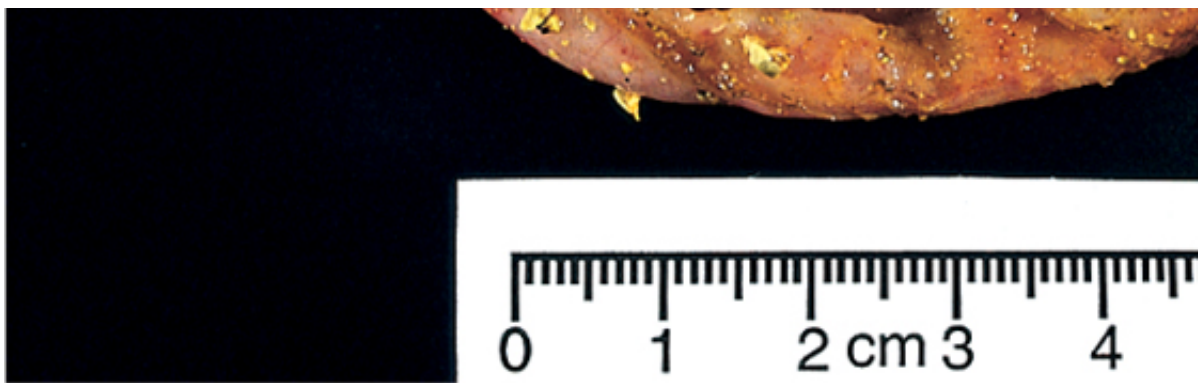
### Morphology

**Cholesterol stones** arise exclusively in the gallbladder and consist of 50% to 100% cholesterol. **Cholesterol stones** are pale yellow; increasing proportions of **calcium carbonate**<sup>®</sup> impart gray-white to black discoloration (Fig. 16-36). They are ovoid and firm; they often there are several, with faceted surfaces resulting from apposition to one another. **Cholesterol stones are radiolucent, although as many as 20% may have sufficient calcium to make them radiopaque.**

**Pigment stones** may arise anywhere in the biliary tree and are trivially classified as black or brown. In general, black pigment stones are found in sterile gallbladder bile, while brown stones are found in intrahepatic or extrahepatic ducts. The stones contain calcium salts of unconjugated bilirubin, as well as small amounts of other calcium salts, mucin glycoproteins, and cholesterol. Black stones are present in large quantities (Fig. 16-37) and crumble easily. Brown stones tend to be solitary and are soft with a greasy, soaplike consistency that results from the presence of cholesterol released by the action of bacterial phospholipases on biliary lecithins. Because of the presence of phosphates, **50% to 75% of black stones are radiopaque.** Brown stones, which are usually radiolucent.

### Clinical Features





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 Figure 16-36 Cholesterol gallstones. Mechanical manipulation during laparoscopic cholecystectomy has caused rupture, revealing interiors that are pigmented because of entrapped bile pigments. The gallbladder mucosa is reddened and inflamed because of chronic cholecystitis.





Figure 16-37 Pigmented gallstones. Several faceted black gallstones are present in this otherwise unremarkable gallbladder, leading to chronic intravascular hemolysis.

Among persons with gallstones, 70% to 80% remain asymptomatic throughout life, while the remainder develop symptoms at a rate of 1% to 3% per year. The risk for the appearance of symptoms diminishes with time. The symptoms are usually excruciating, either constant or "colicky" (spasmodic) from an obstructed gallbladder or when a stone lodges in the biliary tree. Inflammation of the gallbladder, in association with stones, also generates empyema, perforation, fistulae, inflammation of the biliary tree, and obstructive cholestasis or pancreatitis. It is likely that they are to enter the cystic or common ducts to produce obstruction; it is the very small stones that are most likely to do so. Occasionally a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction.

### Cholecystitis

Inflammation of the gallbladder may be acute, chronic, or acute superimposed on chronic, and all are associated with gallstones. In the United States, cholecystitis is one of the most common indications for abdominal surgery. Its occurrence closely parallels that of gallstones.

#### Morphology

In **acute cholecystitis** the gallbladder is usually enlarged (twofold to threefold) and has a bright red or blotchy, violaceous to green-black discoloration, imparted by subserosal hemorrhage. The serosal covering is frequently layered by fibrin and, in severe cases, by a suppurative exudate. If stones are present, often obstructing the neck of the gallbladder or the cystic duct, the lumen is filled with a cloudy or turbid bile that may contain fibrin, blood, and frank pus. If the exudate is virtually pure pus, the condition is referred to as **empyema of the gallbladder**. The gallbladder wall is thickened, edematous, and hyperemic. In more severe cases the gallbladder is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**. The inflammatory reactions are not distinctive and consist of the usual patterns of acute inflammation: edema, leukocytic infiltration, vascular congestion, frank abscess formation, or gangrene.

The morphologic changes in **chronic cholecystitis** are extremely variable and sometimes the mere presence of stones within the gallbladder, even in the absence of acute inflammation, provides sufficient justification for the diagnosis. The gallbladder may be contracted, of normal size, or enlarged. Mucosal ulcerations are infrequent; the submucosa and subserosa are often thickened. In the absence of superimposed acute cholecystitis, mural lymphocytes are the only sentinels.

#### Acute Calculous Cholecystitis

Acute inflammation of a gallbladder that contains stones is termed *acute calculous cholecystitis* and is the most common major complication of gallstones and the most common indication for cholecystectomy. Symptoms may appear with remarkable suddenness and constitute an acute surgical emergency. Symptoms may be mild and resolve without medical intervention.

Acute calculous cholecystitis is initially the result of chemical irritation and inflammation of the gallbladder by bile outflow. The action of phospholipases derived from the mucosa hydrolyzes biliary lecithin to fatty acids and glycerol. The normally protective glycoprotein mucous layer is disrupted, exposing the mucosal epithelium to bile salts. Prostaglandins released within the wall of the distended gallbladder contribute to mucosal edema and increased intraluminal pressure may also compromise blood flow to the mucosa. These events may lead to infection; only later may bacterial contamination develop.

#### Acute Non-Calculous Cholecystitis

Between 5% and 12% of gallbladders removed for acute cholecystitis contain no gallstones. Most patients: (1) the postoperative state after major, nonbiliary surgery; (2) severe trauma (e.g., motor vehicle accident); (3) severe burns; (4) sepsis. Many events are thought to contribute to acute acalculous (non-calculous) cholecystitis.

stasis and sludging, vascular compromise, and, ultimately, bacterial contamination.

### **Chronic Cholecystitis**

Chronic cholecystitis may be the sequel to repeated bouts of acute cholecystitis, but in most instances it follows acute attacks. Like acute cholecystitis it is almost always associated with gallstones. However, gallstones are not always in the initiation of inflammation or the development of pain, because chronic acalculous cholecystitis has alterations similar to those seen in the calculous form. Rather, supersaturation of bile predisposes in most instances, stone formation. Microorganisms, usually *Escherichia coli* and enterococci, can be cultured in a third of cases. Unlike acute calculous cholecystitis, stone obstruction of gallbladder outflow is not always present. Nevertheless, the symptoms of chronic cholecystitis are similar to those of the acute form and range from mild upper quadrant pain and epigastric distress. Because most gallbladders removed at elective surgery have evidence of chronic cholecystitis, one must conclude that biliary symptoms emerge after long-term coexistent inflammation.

### **Clinical Features**

*Acute calculous cholecystitis* may be barely noticeable or may announce itself acutely, with severe pain radiating to the right shoulder. Sometimes, when stones are present in the gallbladder neck or in the cystic duct, leukocytosis, and prostration are classic; the presence of conjugated hyperbilirubinemia suggests that the right subcostal region is markedly tender and rigid as a result of spasm of the abdominal muscles. The gallbladder can be palpated. Mild attacks usually subside spontaneously over 1 to 10 days; however, approximately 25% of symptomatic patients are sufficiently ill to require surgical intervention.

Symptoms arising from *acute acalculous cholecystitis* are usually obscured by the generally severe abdominal pain. Diagnosis therefore rests on keeping this possibility in mind.

*Chronic cholecystitis* does not have the striking manifestations of the acute forms and is usually characterized by steady or colicky epigastric or right upper quadrant pain. Nausea, vomiting, and intolerance for fatty foods are common.

The diagnosis of both acute and chronic cholecystitis usually rests on the detection of gallstones on ultrasonography, typically accompanied by evidence of a thickened gallbladder wall. Attention to the following complications:

- Bacterial superinfection with cholangitis or sepsis
- Gallbladder perforation and local abscess formation
- Peritonitis
- Biliary enteric (cholecystenteric) fistula, with drainage of bile into adjacent organs
- Intestinal obstruction (ileus)
- Aggravation of preexisting pulmonary, renal, or liver decompensation





## DISORDERS OF EXTRAHEPATIC BILE DUCTS

### Choledocholithiasis and Cholangitis

These conditions are considered together because they frequently go hand in hand.

*Choledocholithiasis* is the presence of stones within the biliary tree. In Western nations, almost all stones are derived from the gallbladder; in Asia, there is a much higher incidence of primary ductal and intrahepatic, usually pigmented, stone formation. Choledocholithiasis may not immediately obstruct major bile ducts; asymptomatic stones are found in about 10% of patients at the time of surgical cholecystectomy. Symptoms may develop because of (1) biliary obstruction, (2) pancreatitis, (3) cholangitis, (4) hepatic abscess, (5) chronic liver disease with secondary biliary cirrhosis, or (6) acute calculous cholecystitis.

*Cholangitis* is the term used for acute inflammation of the wall of bile ducts, almost always caused by bacterial infection of the normally sterile lumen. It can result from any lesion obstructing bile flow, most commonly choledocholithiasis, and also from surgical reconstruction of the biliary tree. Uncommon causes include tumors, indwelling stents or catheters, acute pancreatitis, and benign strictures. Bacteria most likely enter the biliary tract through the sphincter of Oddi, rather than by the hematogenous route. *Ascending cholangitis* refers to the propensity of bacteria, once within the biliary tree, to infect intrahepatic biliary ducts. The usual pathogens are *E. coli*, *Klebsiella*, *Clostridium*, *Bacteroides*, or *Enterobacter*; group D streptococci are also common, and two or more organisms are found in half of the cases. In some world populations, parasitic cholangitis is a significant problem: *Fasciola hepatica* or schistosomiasis in Latin America and the Near East, *Clonorchis sinensis* or *Opisthorchis viverrini* in the Far East, and cryptosporidiosis in individuals with acquired immunodeficiency syndrome.

Bacterial cholangitis usually produces fever, chills, abdominal pain, and jaundice. The most severe form of cholangitis is suppurative cholangitis, in which purulent bile fills and distends bile ducts, with an attendant risk of liver abscess formation. Because sepsis rather than cholestasis is the dominant risk in cholangitic patients, prompt diagnosis and intervention are imperative.

### Secondary Biliary Cirrhosis

Prolonged obstruction of the extrahepatic biliary tree results in profound damage to the liver itself. The most common cause of obstruction is extrahepatic cholelithiasis. Other obstructive conditions include biliary atresia (discussed below), malignancies of the biliary tree and head of the pancreas, and strictures resulting from previous surgical procedures. The initial morphologic features of cholestasis were described earlier and are entirely reversible with correction of the obstruction. However, secondary inflammation resulting from biliary obstruction initiates periportal fibrogenesis, which eventually leads to scarring and nodule formation, generating secondary biliary cirrhosis. Subtotal obstruction may promote secondary bacterial infection of the biliary tree (ascending cholangitis), which further contributes to the damage. Enteric organisms such as coliforms and enterococci are common culprits.

### Biliary Atresia

The infant presenting with neonatal cholestasis was discussed previously in the context of neonatal hepatitis. A major contributor to neonatal cholestasis is biliary atresia, accounting for one-third of infants with neonatal cholestasis and occurring in approximately 1 in 10,000 live births. Biliary atresia is defined as a complete obstruction of bile flow caused by destruction or absence of all or part of the extrahepatic bile ducts. It is the most frequent cause of death from liver disease in early childhood and accounts for more than half of the children referred for

liver transplantation.

The salient features of biliary atresia include (1) inflammation and fibrosing stricture of the hepatic or common bile ducts; (2) inflammation of major intrahepatic bile ducts, with progressive destruction of the intrahepatic biliary tree; (3) florid features of biliary obstruction on liver biopsy (i.e., marked bile ductular proliferation, portal tract edema and fibrosis, and parenchymal cholestasis); and (4) periportal fibrosis and cirrhosis within 3 to 6 months of birth.

#### *Clinical Course*

Infants with biliary atresia present with neonatal cholestasis, as discussed earlier; there is a slight female preponderance. They have normal birth weights and postnatal weight gain. Stools change from initially normal to acholic as the disease evolves. Laboratory findings do not distinguish between biliary atresia and intrahepatic cholestasis, but a liver biopsy provides evidence of bile duct obstruction in 90% of cases of biliary atresia. Liver transplantation remains the definitive treatment. Without surgical intervention, death usually occurs within 2 years of birth.

### **SUMMARY**

#### **Diseases of the Gallbladder and Extrahepatic Bile Ducts**

Gallbladder diseases include cholelithiasis and acute and chronic cholecystitis. Gallstone formation is a common condition in Western countries. The great majority of the gallstones are cholesterol stones. Pigmented stones containing bilirubin and calcium are most common in Asian countries. Risk factors for the development of cholesterol stones are advancing age, female gender, estrogen use, obesity, and heredity. Cholecystitis almost always occurs in association with cholelithiasis, although in about 10% of cases it occurs in the absence of gallstones. Acute calculous cholecystitis is the most common reason for emergency cholecystectomy.







## TUMORS

### Carcinoma of the Gallbladder

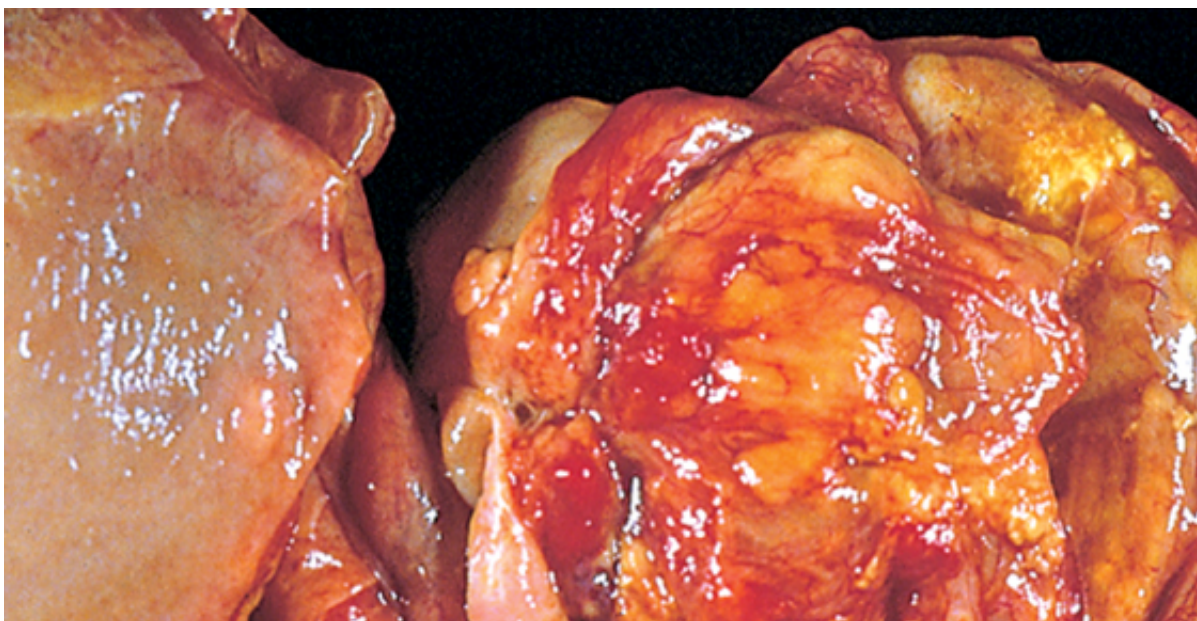
Carcinoma of the gallbladder, which develops from the epithelial lining of the organ, is the most frequent malignancy of the biliary tract. It is slightly more common in women and occurs most frequently in the seventh decade of life. For the United States, the incidence of gallbladder cancer is more frequent in Mexico and Chile. In the United States the incidence is highest in the elderly, and rarely is it discovered at a resectable stage, and the mean 5-year survival has remained at a dismal 5% to 90% of cases. However, in Asia, where pyogenic and parasitic diseases of the biliary tree are more common, gallbladder cancer is more important. Presumably, gallbladders containing stones or infectious agents develop cancer as a result of chronic inflammation. The role of carcinogenic derivatives of bile acids is unclear, but the presence of a adenoma-carcinoma junction is considered to be a risk factor.

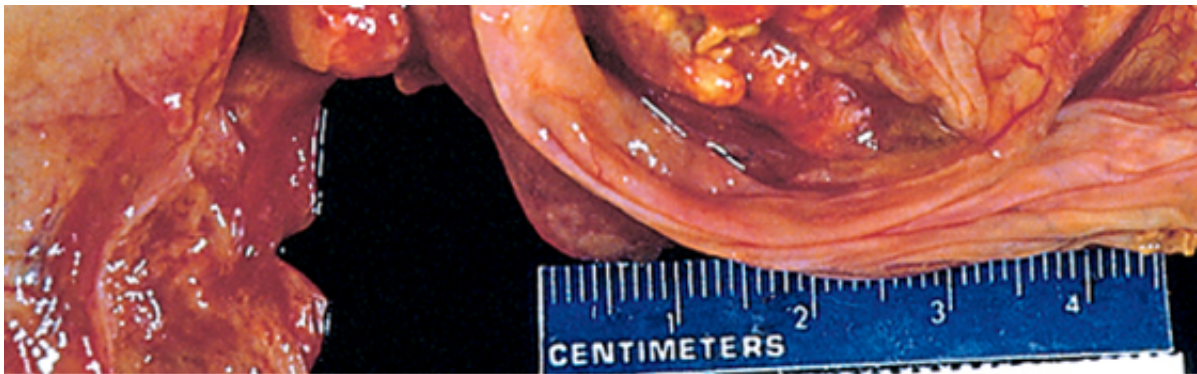
#### Morphology

Cancers of the gallbladder assume either **exophytic** or **infiltrating** patterns of growth. The infiltrating pattern is more common and usually appears as a poorly defined area of diffuse thickening of the gallbladder wall that may cover several square centimeters or involve the entire gallbladder. The exophytic pattern grows into the lumen as an irregular mass. Both patterns are scirrhous and very firm. The exophytic pattern grows into the lumen as an irregular mass, and at the same time it invades the underlying wall (Fig. 16-38). **Most carcinomas of the gallbladder are adenocarcinomas.** They may be papillary, poorly differentiated, or undifferentiated (Fig. 16-39). About 5% are squamous cell carcinomas or have adenosquamous differentiation. Carcinoid tumors are rare. By the time gallbladder cancers are discovered, **most have invaded the liver.** Many have extended to the cystic duct and adjacent bile ducts and portal hepatic lymphatics. Metastases to the peritoneum, gastrointestinal tract, and lungs are less common sites of seeding.

#### Clinical Features

Preoperative diagnosis of carcinoma of the gallbladder is the exception, occurring in fewer than 20% of cases. The disease is insidious and typically indistinguishable from those associated with cholelithiasis: abdominal pain, weight loss, and vomiting. The fortunate person develops early obstruction and acute cholecystitis before extensive metastatic disease. The person undergoes cholecystectomy for coexistent symptomatic gallstones. Preoperative diagnosis rests largely on imaging studies with abnormalities in the gallbladder wall documented by imaging studies.

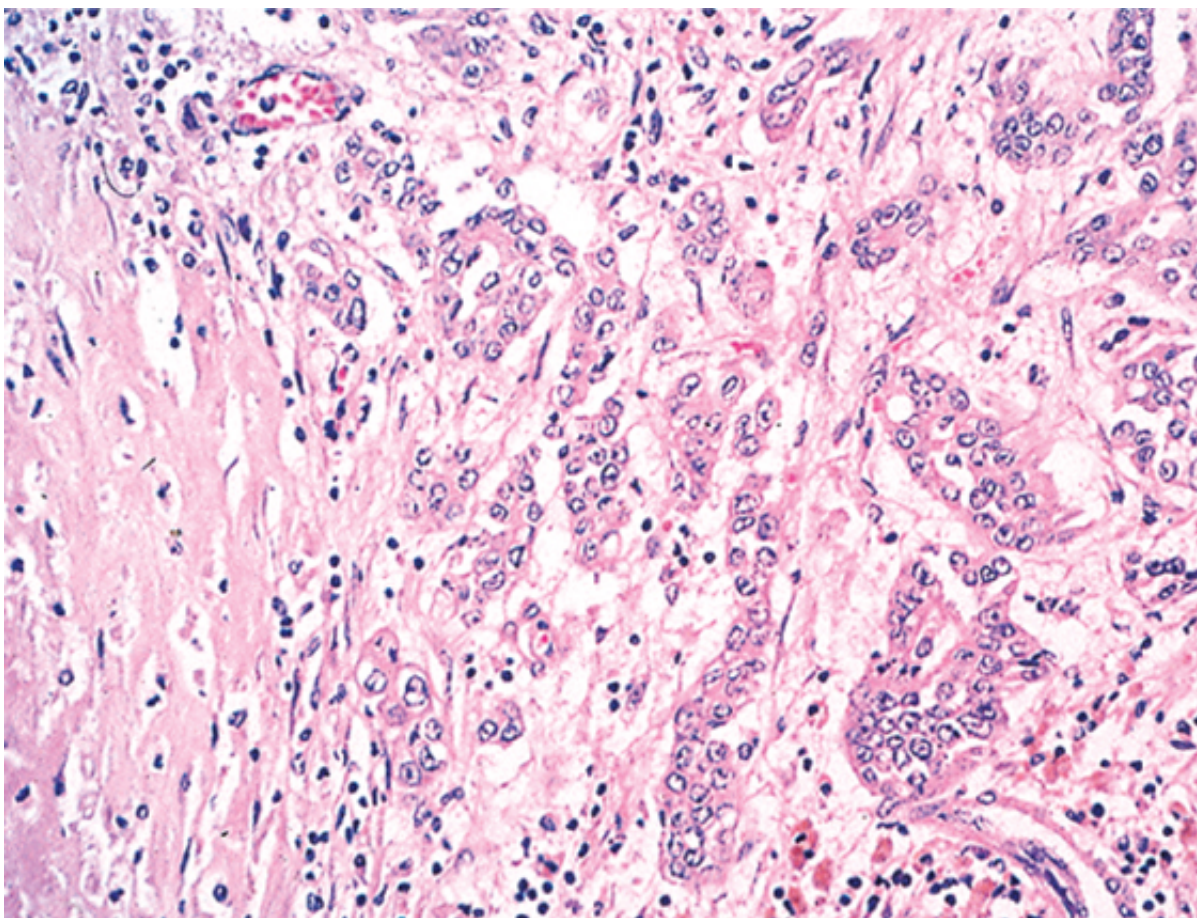




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Figure 16-38 Adenocarcinoma of the gallbladder. The opened gallbladder contains a large, exophytic

### **Cholangiocarcinomas**

Cholangiocarcinomas are adenocarcinomas with biliary differentiation arising from cholangiocytes. Extrahepatic cholangiocarcinomas, constituting approximately two-thirds of these tumors, may develop in the bile ducts (extrahepatic) or more distally in the biliary tree, as far as the peripancreatic portion of the distal common bile duct (intrahepatic). They occur mostly in individuals of 50 to 70 years of age. Because both intra- and extrahepatic cholangiocarcinomas often reach an advanced stage, the prognosis is poor and most patients have unresectable tumors. Risk factors for cholangiocarcinoma include chronic cholangitis (already described), fibrocystic diseases of the biliary tree, and exposure to Thorotrast (a radioactive contrast agent of the biliary tree). The incidence of intrahepatic cholangiocarcinomas is increasing worldwide, while the incidence of extrahepatic cholangiocarcinomas has decreased. The causes for these changes in incidence are unknown, but they suggest that intra- and extrahepatic cholangiocarcinomas have different pathogenesis.







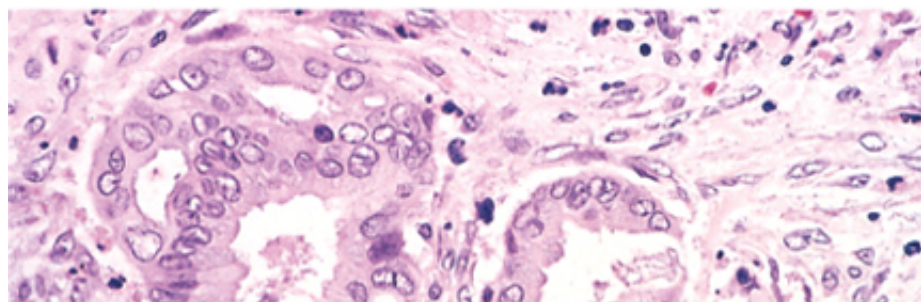
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 Figure 16-39 Adenocarcinoma of the gallbladder. Malignant glandular structures are present within the

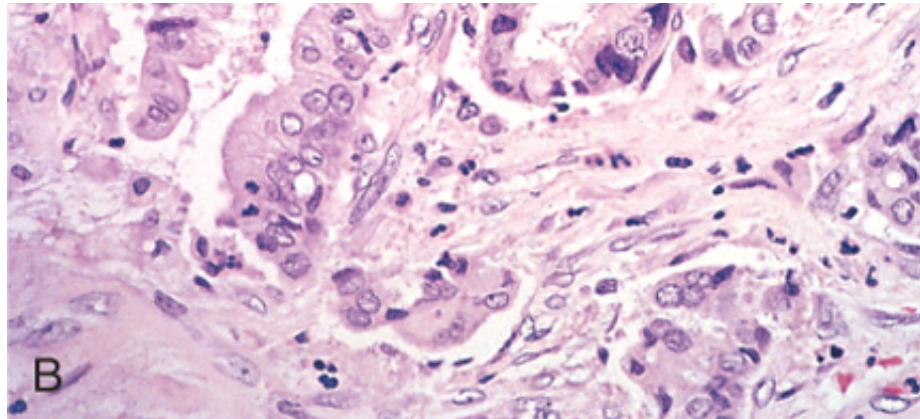
### Morphology

**Cholangiocarcinomas** appear as more or less well-differentiated adenocarcinomas with abundant fibrous stroma (desmoplasia) explaining their firm, gritty consistency (Fig 16-39). They form clearly defined glandular and tubular structures lined by somewhat anaplastic cuboidal to columnar epithelial cells. Bile pigment and hyaline inclusions are not found within the cells.

Because partial or complete obstruction of bile ducts rapidly leads to jaundice, extrahepatic cholangiocarcinomas tend to be relatively small at the time of diagnosis. Most appear as firm, gray nodules. Some may be diffusely infiltrative lesions, creating ill-defined thickening of the wall; others are polypoid lesions. Uncommonly, squamous features are present. For the most part, the stroma accompanies the epithelial proliferation. Cholangiocarcinomas may spread to regional lymph nodes, lungs, bones, and adrenal glands. Cholangiocarcinoma has less extrahepatic spread than hepatocellular carcinomas.

### Pathogenesis and Clinical Features





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Figure 16-40 Cholangiocarcinoma. **A**, Massive neoplasm in the right lobe and multiple metastases throughout the surrounding liver parenchyma, surrounded by dense sclerotic stroma.

The feature common to the risk factors for cholangiocarcinomas is that they all cause chronic cholestasis. The pathogenesis of cholangiocarcinomas in humans and experimental animals have demonstrated several mechanisms, including overexpression of the tyrosine kinase receptors ErbB-2 and c-met, up-regulation of cyclin D1, and increased frequency of abnormalities in the *p16* tumor suppressor gene. ErbB-2 and COX-2 inhibitors are being evaluated as therapeutic agents.

Intrahepatic cholangiocarcinoma is detected by the presence of a liver mass and unspecific symptoms such as weight loss and ascites. Symptoms arising from extrahepatic cholangiocarcinomas (jaundice, decolorization of stool, and weight loss) result from biliary obstruction. Associated changes are elevated levels of serum alkaline phosphatase, bile-stained urine, and prolonged prothrombin time. Surgical resection is the only treatment available. Survival times range from 6 to 18 months, regardless of whether aggressive resection or palliative

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## 17 The Pancreas\*

The pancreas has critical endocrine functions, and the exocrine portion of the pancreas is a major source of extremely potent digestive enzymes. Consequently, diseases affecting the pancreas can wreak major havoc and can be the source of significant morbidity and mortality. A general truism from the practice of surgery is particularly apt: "You don't mess around with the pancreas." Unfortunately, despite its physiologic importance, the retroperitoneal location of the pancreas and the generally vague signs and symptoms associated with its injury allow many pancreatic diseases to progress undiagnosed for extended periods of time; recognition of disease often requires a high degree of suspicion.

The adult pancreas is a transversely oriented retroperitoneal organ extending from the "C" loop of the duodenum to the hilum of the spleen. Although the pancreas does not have well-defined anatomic subdivisions, adjacent vessels and ligaments can demarcate the organ into a head, body, and tail.

The pancreas gets its name from the Greek *pankreas*, meaning "all flesh." It is, however, a complex lobulated organ with distinct endocrine and exocrine elements. The endocrine portion constitutes only 1% to 2% of the pancreas and is composed of about 1 million cell clusters, the islets of Langerhans; these cells secrete insulin, glucagon, and somatostatin. The most significant disorders of the *endocrine* pancreas include diabetes mellitus and neoplasms; these are described in detail in [Chapter 20](#) and will not be discussed further here.

The *exocrine pancreas* is composed of *acinar cells* that produce the digestive enzymes, and the ductules and ducts that convey them to the duodenum. The acinar cells produce mostly proenzyme forms of digestive enzymes and store them in membrane-bound *zymogen granules*. When acinar cells are stimulated to secrete, the granules fuse with the apical plasma membrane and release their contents into the central acinar lumen.

These secretions are transported to the duodenum through a series of anastomosing ducts. The epithelial cells lining the ducts are also active participants in pancreatic secretion: cuboidal epithelial cells lining the smaller ductules secrete bicarbonate-rich fluid, while the columnar epithelial cells lining the larger ducts produce mucin. The epithelial cells of the larger pancreatic ducts express the *cystic fibrosis transmembrane conductance regulator (CFTR)*; aberrant expression of this membrane protein affects the viscosity of the pancreatic secretions and has a fundamental role in the pathophysiology of pancreatic disease in persons with cystic fibrosis ([Chapter 7](#)).

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In general, the exocrine products of the pancreas are secreted as enzymatically inert proenzymes (e.g. trypsinogen); amylase and lipase are exceptions and are secreted in an active form. The strategy of producing most pancreatic enzymes in an inactive zymogen form is largely to prevent self-digestion; it also focuses the eventual work of the activated enzymes to the duodenal lumen. The proenzymes remain largely inactive until they reach the duodenum; there, enteropeptidase (a brush-border enzyme) cleaves trypsinogen into active trypsin. Activated trypsin then functions to catalyze the cleavage of the other proenzymes.

As we will see, autodigestion of the pancreas (e.g., in pancreatitis) can be a catastrophic event. Thus, a number of "fail-safe" mechanisms have evolved to minimize the risk of this occurring:

The majority of pancreatic enzymes are synthesized as inactive proenzymes. The proenzymes are sequestered in membrane-bound zymogen granules. Activation of

proenzymes are sequestered in membrane-bound zymogen granules. Activation of proenzymes requires conversion of trypsinogen to trypsin by duodenal enteropeptidase (enterokinase). Trypsin inhibitors (e.g., serine protease inhibitor Kazal type I or SPINK1) are also secreted by acinar and ductal cells. Trypsin contains a critical self-recognition cleavage site that allows trypsin to inactivate itself in situations wherein there is a high local concentration of activated enzyme. Most of the secreted enzymes have acidic pH optima and are relatively inactive in the bicarbonate-rich pancreatic fluid. Enzymes within lysosomes can degrade zymogen granules if normal acinar secretion is blocked. Acinar cells are remarkably resistant to the action of activated enzymes such as trypsin, [chymotrypsin](#)<sup>®</sup>, and phospholipase A<sub>2</sub>.

Diseases of the exocrine pancreas include cystic fibrosis, congenital anomalies, acute and chronic pancreatitis, and neoplasms. Cystic fibrosis is discussed in detail in [Chapter 7](#); the remainder of this chapter will discuss the other pathologic processes.



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## CONGENITAL ANOMALIES

Pancreatic development is a complex process involving fusion of dorsal and ventral primordia; subtle deviations in this process frequently give rise to congenital variations in pancreatic anatomy. While most of these do not cause disease per se, variants (especially in ductal anatomy) can present unique challenges to the endoscopist and surgeon. For example, failure to recognize idiosyncratic anatomy could conceivably result in inadvertent severing of a pancreatic duct during surgery, resulting in pancreatitis.

### Agenesis

Very rarely, the pancreas may be totally absent, a condition usually (but not invariably) associated with additional severe malformations that are incompatible with life. *IPF1* is a homeodomain transcription factor critical for normal pancreas development, and *IPF1* gene mutations on chromosome 13q12.1 have been associated with pancreatic agenesis.

*Pancreas divisum* is the most common clinically significant congenital pancreatic anomaly, with an incidence of 3% to 10%. It occurs when the fetal duct systems of the pancreatic primordia fail to fuse. As a result, the main pancreatic duct (Wirsung) is very short and drains only a small portion of the head of the gland, while the bulk of the pancreas (from the dorsal pancreatic primordium) drains through the minor sphincter. The relative stenosis caused by the bulk of the pancreatic secretions passing through the minor sphincter predisposes such individuals to chronic pancreatitis.

*Annular pancreas* is a relatively uncommon variant on pancreatic fusion; the outcome is a ring of pancreatic tissue that completely encircles the duodenum. It can present with signs and symptoms of duodenal obstruction such as gastric distention and vomiting.

### Ectopic Pancreas

Aberrantly situated, or *ectopic*, pancreatic tissue occurs in about 2% of the population; favored sites are the stomach and duodenum, followed by the jejunum, Meckel diverticulum, and ileum. These embryologic rests are typically small (millimeters to centimeters in diameter) and are located in the submucosa; they are composed of normal pancreatic acini with occasional islets. Though usually incidental and asymptomatic, ectopic pancreas can cause pain from localized inflammation, or-rarely-can cause mucosal bleeding. Approximately 2% of islet cell tumors arise in ectopic pancreatic tissue.

*Congenital cysts* probably result from anomalous ductal development. In *polycystic disease*, kidney, liver, and pancreas can all contain cysts (see [Chapter 14](#)). Pancreatic cysts range from microscopic to 5 cm in diameter. They are lined by duct-type cuboidal epithelium or can lack a cell lining altogether, and are enclosed in a thin, fibrous capsule. In general, unilocular cysts tend to be benign, while multilocular cysts are more often neoplastic and possibly malignant (see below).







## PANCREATITIS

Inflammation of the pancreas can have clinical manifestations ranging from mild, self-limited disease to a destructive process; durations can vary from transient to irreversible loss of function. By definition, acute pancreatitis returns to normal if the underlying cause of inflammation is removed. In contrast, *chronic pancreatitis* is characterized by irreversible destruction of exocrine pancreatic parenchyma.

### Acute Pancreatitis

Acute pancreatitis is a group of reversible lesions characterized by inflammation; severity can range from mild inflammation to widespread parenchymal necrosis with severe hemorrhage. Acute pancreatitis is relatively common in industrialized countries of 10 to 20 per 100,000 people. Approximately 80% of cases are attributable to alcoholism ([Table 17-1](#)). Roughly 5% of patients with gallstones develop acute pancreatitis, and 5% of cases overall. Excessive alcohol intake as a cause of acute pancreatitis varies from 65% of cases in the United States to 10% in the United Kingdom.

**Table 17-1. Etiologic Factors in Acute Pancreatitis**

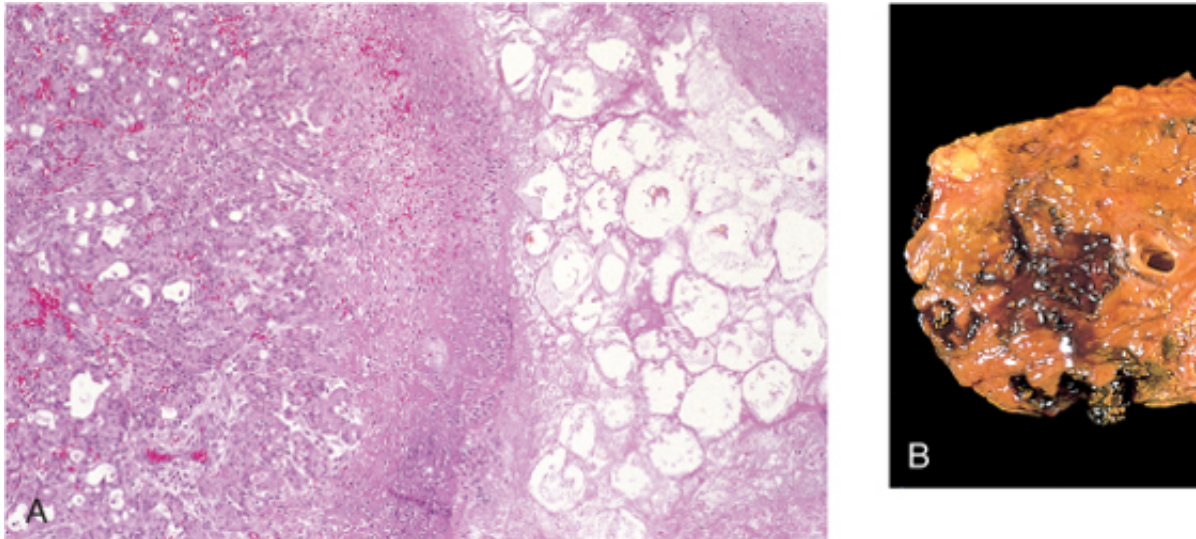
<b>Metabolic</b>
Alcoholism
Hyperlipoproteinemia
Hypercalcemia
Drugs (e.g., thiazide diuretics)
Genetic
<b>Mechanical</b>
Trauma
Gallstones
Iatrogenic injury
Perioperative injury
Endoscopic procedures with dye injection
<b>Vascular</b>
Shock
Atheroembolism
Polyarteritis nodosa
<b>Infectious</b>
Mumps
Coxsackievirus
<i>Mycoplasma pneumoniae</i>

Other causes of acute pancreatitis include:

Non-gallstone obstruction of the pancreatic ducts (e.g., due to periampullary tumors, pancreatic parasites—generally *Ascaris lumbricoides*) Medications including thiazide diuretics, [azathioprine](#), [furosemide](#), [methyldopa](#), pentamidine, and procainamide Infections with mumps, coxsackievirus, *Mycoplasma pneumoniae* Metabolic disorders, including hypertriglyceridemia, hyperparathyroidism, and hypocalcemia Vascular thrombosis, embolism, vasculitis, or shock Trauma, both blunt force and iatrogenic Genetic mutations in genes encoding pancreatic enzymes or their inhibitors (e.g., *SPINK1*). For example, *SPINK1* is an autosomal dominant disease with an 80% penetrance characterized by recurrent attacks of pancreatitis starting in childhood. It is caused by mutations in the *PRSS1* gene that affect a site on the trypsinogen

cleavage (inactivation) of trypsin by trypsin itself. When this site is mutated, trypsinogen an leading to ongoing activation of other digestive proenzymes, and eventually the developme

Notably, 10% to 20% of patients with acute pancreatitis have no identifiable cause (*idiopathic pan* evidence suggests that many may have an underlying genetic basis.



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Figure 17-1 Acute pancreatitis. **A**, The microscopic field shows a region of fat necrosis (*right*), and focal pancreatic hemorrhage in the pancreatic substance and a focal ar (*upper left*).

### Morphology

The morphology of acute pancreatitis ranges from trivial inflammation and edema t hemorrhage. The basic alterations are **(1) microvascular leakage causing edem lipases, (3) an acute inflammatory reaction, (4) proteolytic destruction of pan (5) destruction of blood vessels with hemorrhage.**

In milder forms, histologic alterations include interstitial edema and focal areas of f pancreatic substance and peripancreatic fat (**Fig. 17-1A**). Fat necrosis results from fat cells; the released fatty acids combine with calcium to form insoluble salts that p

In more severe forms, such as **acute necrotizing pancreatitis**, necrosis of pancre and ductal tissues as well as the islets of Langerhans; vascular damage causes he parenchyma of the pancreas. Macroscopically, the pancreas exhibits red-black her foci of yellow-white, chalky fat necrosis (**Fig. 17-1B**). Fat necrosis can also occur in including the omentum and bowel mesentery, and even outside the abdominal cav fat). In most cases the peritoneum contains a serous, slightly turbid, brown-tinged f (derived from enzymatically digested adipose tissue). In the most severe form, **her** extensive parenchymal necrosis is accompanied by diffuse hemorrhage.

### Pathogenesis

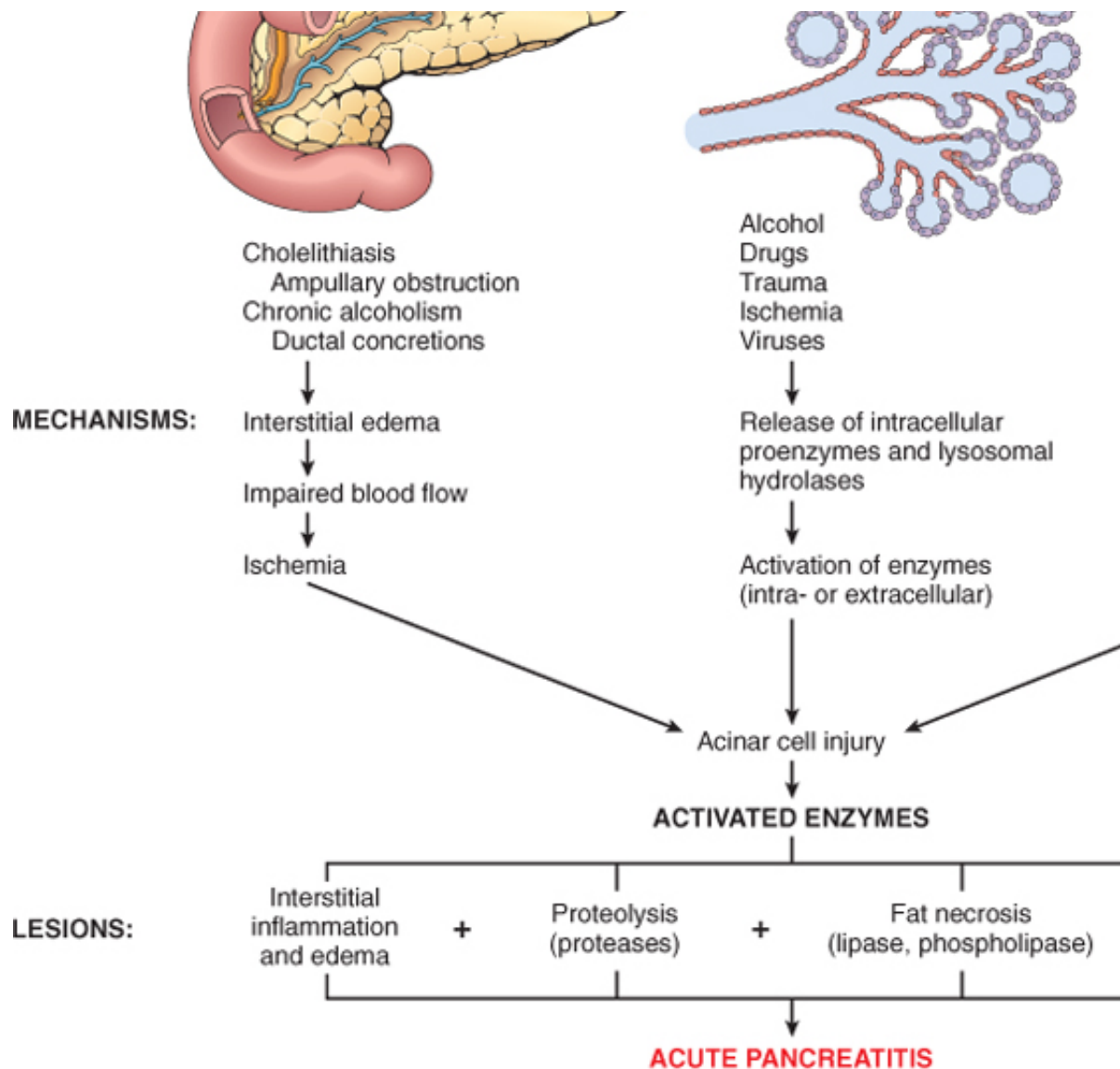
#### CAUSES:

#### DUCT OBSTRUCTION



#### ACINAR CELL INJURY





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Figure 17-2 Proposed pathogenesis of acute pancreatitis.

The histologic changes seen in acute pancreatitis strongly suggest *autodigestion of the pancreatic enzymes*. Recall that the zymogen forms of pancreatic enzymes must be enzymatically activated. Central in this process and *activation of trypsin is thus a critical triggering event in acute pancreatitis*. Once activated from its proenzyme trypsinogen, it can activate other proenzymes (e.g., phospholipases and elastase), thus setting in motion the process of autodigestion. Trypsin also converts prekallikrein to its activated form, thus sparking the intrinsic pathway of the complement system (Chapter 4). Three enzyme activation that may lead to acute pancreatitis (Fig. 17-2):

**Pancreatic duct obstruction.** Impaction of a gallstone or biliary sludge, or extrinsic compression blocks ductal flow, increases intraductal pressure, and allows accumulation of an enzyme-secreting in an active form, this can cause local fat necrosis. Injured tissues, periacinar myofibroblasts, and pro-inflammatory cytokines that promote local inflammation, and interstitial edema through compromised local blood flow, causing vascular insufficiency and ischemic injury to acinar cells. This pathogenic mechanism comes into play in acute pancreatitis caused by ischemia, viruses (e.g., mumps), or toxins (e.g., alcohol). **Defective intracellular transport of proenzymes within acinar cells.** In normal

for zymogen granules (and eventually extracellular release) and hydrolytic enzymes destined to discrete pathways after synthesis in the ER. However, at least in some animal models of acute pancreatitis, trypsin and lysosomal hydrolases become packaged together. This results in proenzyme activation (e.g., trypsinogen to trypsin, phospholipases), and local release of activated enzymes. It is not clear how extensive a role this plays in human pancreatitis, although aberrant acinar cell packaging of digestive enzymes has been demonstrated.

*The manner by which alcohol causes pancreatitis is unknown*, although abnormal proenzyme trafficking is implicated. Other proposed mechanisms include contraction of the sphincter of Oddi (the muscle in the duodenum that controls the flow of pancreatic juice) and direct toxic effects on acinar cells. Alcohol ingestion also causes increased secretion of pancreatic juice, leading to deposition of inspissated protein plugs and obstruction of small pancreatic ducts, followed by inflammation as described above.

### **Clinical Features**

*Abdominal pain* is the cardinal manifestation of acute pancreatitis. Its severity varies from mild and self-limiting to incapacitating. Suspected acute pancreatitis is primarily diagnosed by the presence of elevated plasma amylase and lipase levels, the exclusion of other causes of abdominal pain.

*Full-blown acute pancreatitis is a medical emergency of the first magnitude.* Such individuals usually present with an "acute abdomen" with a painful, rigid abdomen and the ominous absence of bowel sounds. The pain is usually intense and is often referred to the upper back; it must be differentiated from other causes such as a perforated peptic ulcer, acute cholecystitis with rupture, and occlusion of mesenteric vessels with infarction of the small intestine.

*The manifestations of severe acute pancreatitis are attributable to systemic release of digestive enzymes and a systemic inflammatory response.* Patients show increased vascular permeability, leukocytosis, disseminated intravascular coagulation, respiratory distress syndrome (due to alveolar capillary injury), and diffuse fat necrosis. *Peripneumonia* ensues as a result of electrolyte disturbances and loss of blood volume, compounded by endotoxemia (leakage of endotoxin between gastrointestinal flora and the bloodstream), and a massive release of cytokines and vasoactive substances.

*Laboratory findings* include markedly elevated serum amylase during the first 24 hours, followed by a gradual decline to normal levels. Hypocalcemia can result from precipitation of calcium in the extensive areas of fat necrosis. The enlarged inflamed pancreas can be visualized by computed tomography (CT) or magnetic resonance imaging (MRI).

The crux of the management of acute pancreatitis is supportive therapy (e.g., maintaining blood pressure, fluid resuscitation, and "resting" the pancreas by total restriction of food and fluids). In 40% to 60% of cases of acute necrotizing pancreatitis, the pancreas becomes infected, usually by gram-negative organisms from the alimentary tract, further complicating the picture. In most individuals with acute pancreatitis eventually recover, some 5% die from shock during the first week. Multiple organ dysfunction syndrome and acute renal failure are ominous complications. In surviving patients, sequelae include *pancreatic pseudocysts* (see below).

### **Pancreatic Pseudocysts**

A common sequela of acute pancreatitis is a *pancreatic pseudocyst*. Liquefied areas of necrotic pancreatic tissue are walled off by fibrous tissue to form a cystic space, lacking an epithelial lining (hence the prefix "pseudo"). Drainage of this space over months to years (from damaged pancreatic ducts) can cause massive enlargement of the cyst. Approximately 75% of all pancreatic cysts. While many pseudocysts spontaneously resolve, they can persist. Larger pseudocysts can compress or even perforate into adjacent structures.

#### **Morphology**

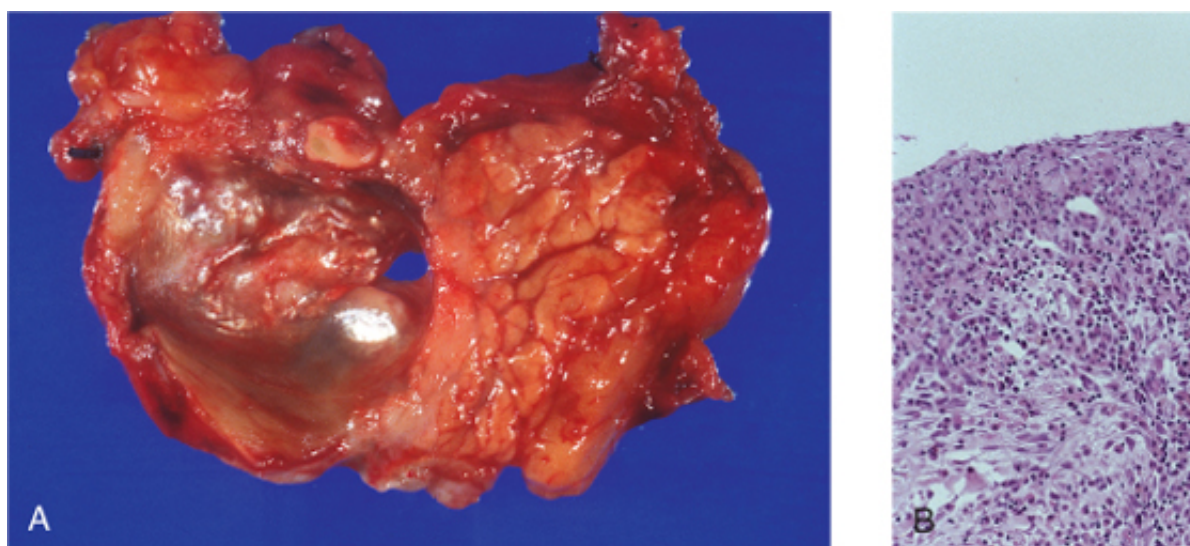
Pseudocysts are usually solitary; they are commonly attached to the surface of the peripancreatic tissues such as the lesser omental sac or the retroperitoneum between the pancreas and the transverse colon or liver (Fig. 17-3A). They can range from 2 to 30 cm in diameter. They are typically composed of necrotic debris walled off by fibrous walls of granulation tissue lacking an epithelial lining (Fig. 17-3B).

### **Chronic Pancreatitis**



Chronic pancreatitis is characterized by longstanding inflammation and fibrosis of the pancreas. In its late stages, the endocrine parenchyma is also lost. Although chronic pancreatitis can result from various causes, *the chief distinction between acute and chronic pancreatitis is the irreversible impairment in pancreatic function*. The prevalence of chronic pancreatitis is difficult to determine but probably ranges between 0.04% and 0.1%. A *common cause of chronic pancreatitis is long-term alcohol abuse*; middle-aged males constitute the majority of cases. Other causes of chronic pancreatitis include:

Long-standing pancreatic duct *obstruction* (e.g., by pseudocysts, calculi, neoplasms, or pancreas divisum, a poorly characterized disorder seen in Africa and Asia, attributed to malnutrition), *hereditary pancreatitis* (see above), or mutations in the *SPINK1* gene encoding trypsin inhibitor. *Chronic pancreatitis as discussed in detail in Chapter 7*, cystic fibrosis is caused by mutations in the *CFTR* gene. *CFTR* is expressed in pancreatic ductal epithelium, and *CFTR* mutations decrease bicarbonate secretion, leading to duct plugging. In typical cystic fibrosis (with  $\Delta 508$  mutation, *Chapter 7*) the secretory defects in the pancreas give rise to pancreatic atrophy early in the course of the disease, rather than progressing to chronic pancreatitis. Individuals with certain *CFTR* mutations develop chronic pancreatitis; interestingly, *the other features of cystic fibrosis are typically absent, and the sweat chloride level is normal*. The mutations of the *CFTR* gene are also associated with cystic fibrosis. Alternatively, *CFTR*-related pancreatitis can also be seen in individuals with *CFTR* gene mutations (compound heterozygotes).



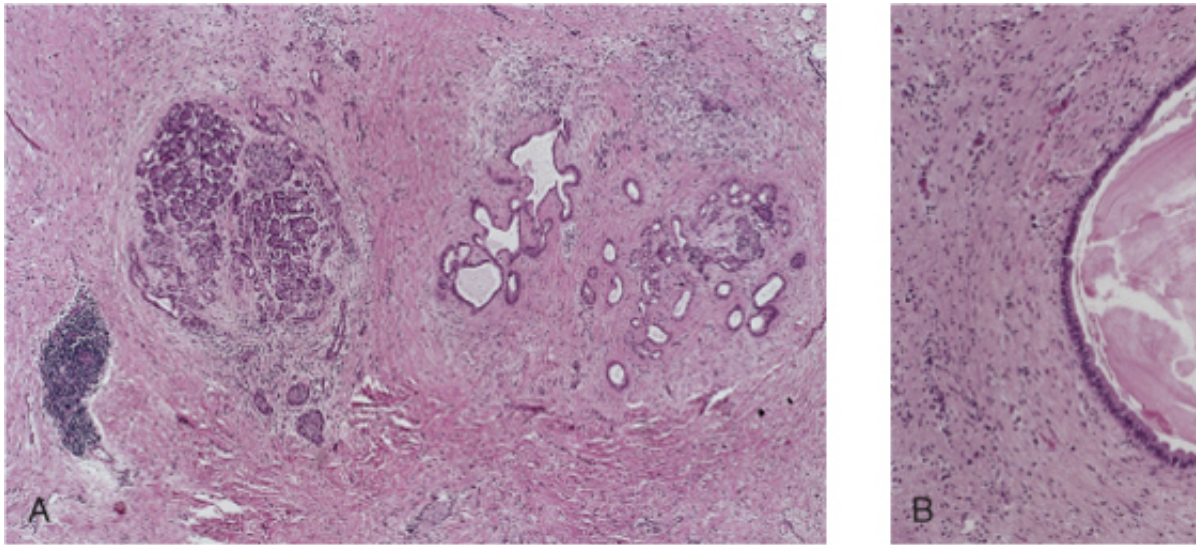
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Figure 17-3 Pancreatic pseudocyst. **A**, Cross-section revealing a poorly defined cyst with a necrotic brownish wall lining and instead is lined by fibrin, granulation tissue, and chronic inflammation.

As many as 40% of individuals with chronic pancreatitis have no recognizable predisposing factor. A growing number of these "idiopathic" cases are associated with inherited mutations in genes implicated in pancreatic function.

### Morphology

Chronic pancreatitis is characterized by **parenchymal fibrosis**, reduced number and size of **pancreatic islets**, and **dilation of the pancreatic ducts**; there is a relative sparing of the islets of Langerhans. **Acinar loss** is a constant feature, usually with a chronic inflammatory infiltrate around the ducts. The ductal epithelium may be atrophied, hyperplastic, or exhibit squamous metaplasia. **Concretions** can occur (*Fig. 17-4B*). The remaining islets of Langerhans become smaller and may fuse and appear enlarged; eventually they also disappear. Grossly, the pancreas is sometimes with extremely dilated ducts and visible calcified concretions.

## Pathogenesis



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Figure 17-4 Chronic pancreatitis. **A**, Extensive fibrosis and atrophy has left only residual islets (*left*) and ducts (*right*) and acinar tissue. **B**, A higher power view demonstrating dilated ducts with inspissated eosinophilic concretions

Although the pathogenesis of chronic pancreatitis is not well defined, several hypotheses are proposed.

**Ductal obstruction by concretions.** Many of the inciting agents in chronic pancreatitis (e.g., concentration of pancreatic secretions, and these proteins can form ductal plugs. **Toxic-metabolites**, can exert a direct toxic effect on acinar cells, leading to lipid accumulation, acinar fibrosis. **Oxidative stress.** Alcohol-induced oxidative stress may generate free radicals in acinar cells, leading to oxidation and subsequent chemokine expression that recruits mononuclear inflammatory cells. Fusion of lysosomes and zymogen granules with resulting acinar cell necrosis, inflammation. Chronic pancreatitis can cause local periductal fibrosis, duct distortion, and altered pancreatic secretions; this can lead to loss of pancreatic parenchyma and fibrosis.

## Clinical Features

Chronic pancreatitis can present in several different ways. It may announce itself with repeated bouts of persistent or recurrent abdominal and back pain, or it may be entirely silent until pancreatic insufficiency develops (usually due to islet destruction). Attacks can be precipitated by alcohol abuse, overeating (increases pancreatic secretion), or opiates or other drugs that increase the muscle tone of the sphincter of Oddi.

**The diagnosis of chronic pancreatitis requires a high degree of suspicion.** During an attack of abdominal pain, there may be modest elevations of serum amylase. In end-stage disease, however, acinar destruction may preclude amylase elevation. Gallstone-induced obstruction may present as jaundice or elevations in serum levels of alkaline phosphatase. Visualization of calcifications within the pancreas by CT or ultrasonography. Weight loss and hypocalcemia caused by pancreatic exocrine insufficiency can also point toward the disease.

Although chronic pancreatitis is usually not acutely life-threatening, the long-term outlook for individuals with the disease is poor, with a 50% mortality rate over 20 to 25 years. Severe **pancreatic exocrine insufficiency** and chronic **diabetes mellitus**. In other patients, **severe chronic pain** may dominate. **Pancreatic pseudocysts** (collections of pancreatic secretions) can develop in some patients. Individuals with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer. The contribution of chronic pancreatitis to cancer development is unclear.

## SUMMARY

**Pancreatitis** *Acute pancreatitis* is characterized by inflammation and reversi with lesions ranging from focal edema and fat necrosis to widespread paren hemorrhage; clinical manifestations vary from mild abdominal pain to a rapid collapse. *Chronic pancreatitis* is characterized by irreversible parenchymal d formation; clinical manifestations include chronic malabsorption (due to pan insufficiency) and diabetes mellitus (due to islet cell loss). Both entities share mechanism, and indeed recurrent acute pancreatitis can result in chronic pa obstruction and alcohol are the most common causes of both forms. Inappri pancreatic digestive enzymes (due to mutations in genes encoding trypsino and primary acinar injury (due to toxins, infections, ischemia, or trauma) als



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## PANCREATIC NEOPLASMS

Pancreatic exocrine neoplasms can be cystic or solid; some are benign, while others are among the

### **Cystic Neoplasms**

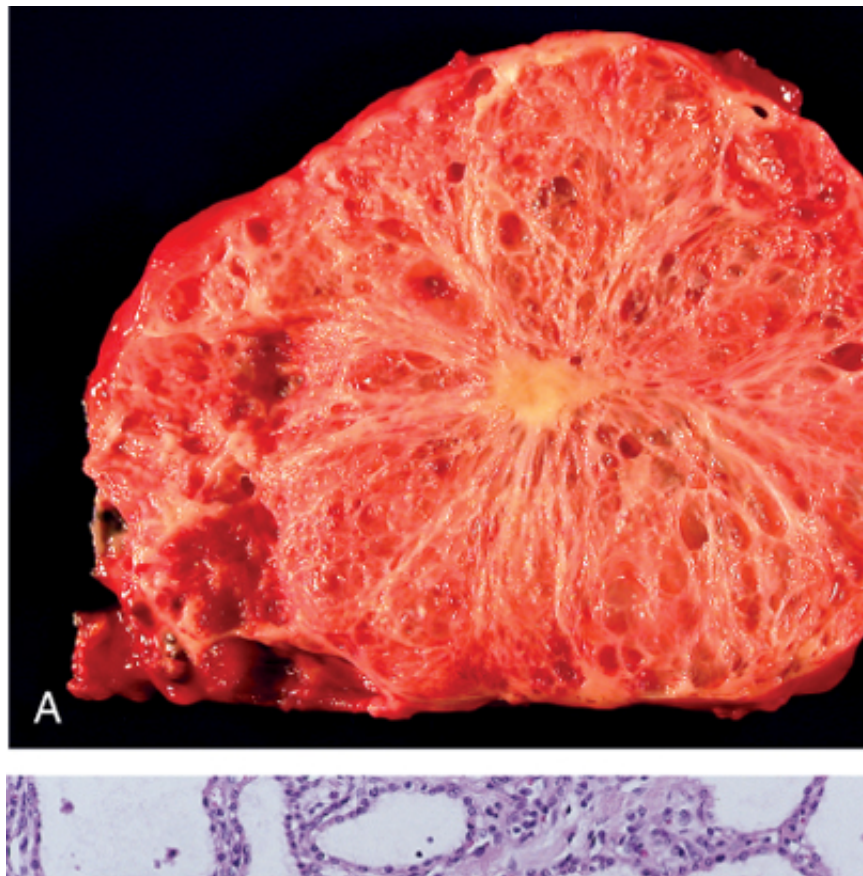
Roughly 5% to 15% of all pancreatic cysts are neoplastic; these constitute less than 5% of all pancreatic neoplasms. Some are entirely benign (e.g., serous cystadenoma); others, such as mucinous cystic neoplasms, can be biologically aggressive with malignant potential.

#### ***Serous Cystadenomas***

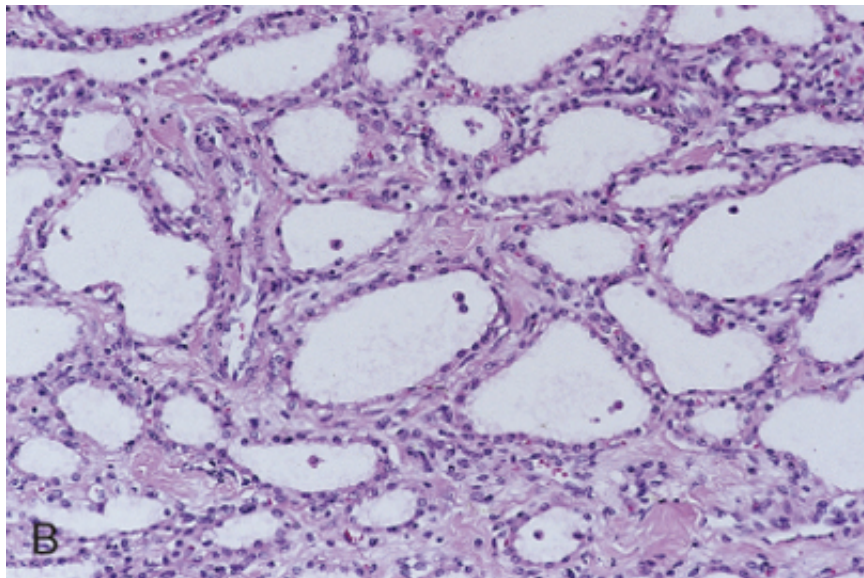
*Serous cystadenomas* account for about a quarter of all pancreatic cystic neoplasms; they are composed of a central scar surrounded by numerous small cysts containing clear, straw-colored fluid (Fig. 17-5). The tumors typically present with nonspecific symptoms such as abdominal pain; the female-to-male ratio is 2 : 1. These tumors are benign, and resection is curative in the vast majority of patients.

#### ***Mucinous Cystic Neoplasms***

*Mucinous cystic neoplasms* almost always arise in women, usually in the body or tail of the pancreas, and are characterized by large, irregularly shaped cysts containing thick, tenacious mucin. The cysts are lined by a simple cuboidal epithelium and are associated with a densely cellular stroma (Fig. 17-6). These tumors can be benign, borderline malignant, or malignant. Benign mucinous cystadenomas lack significant cytologic or architectural atypia, while borderline mucinous cystic neoplasms show architectural atypia but no tissue invasion. Malignant mucinous cystadenocarcinomas are invasive







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 Figure 17-5 Serous cystadenoma. **A**, Cross-section through a serous cystadenoma. Only a thin rim of normal p  
 relatively small and contain clear, straw-colored fluid. **B**, The cysts are lined by cuboidal e

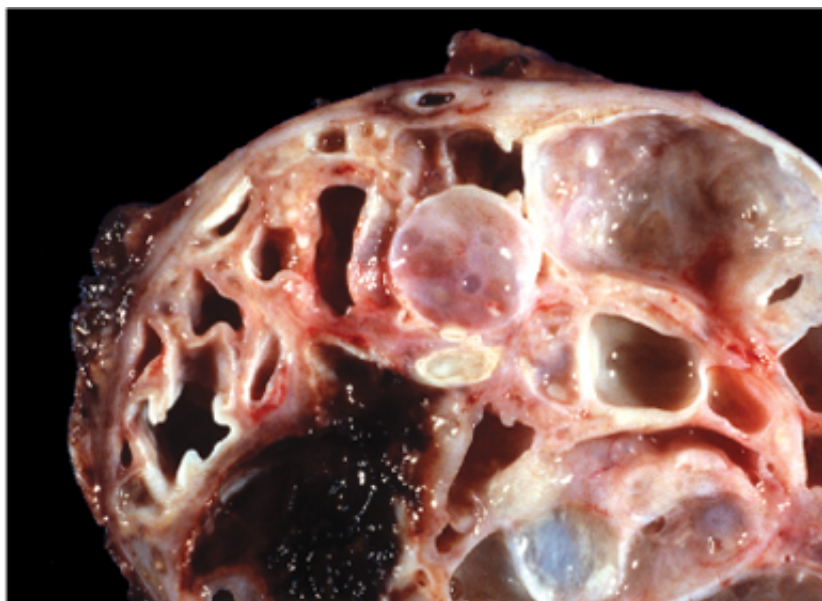
### ***Intraductal Papillary Mucinous Neoplasms***

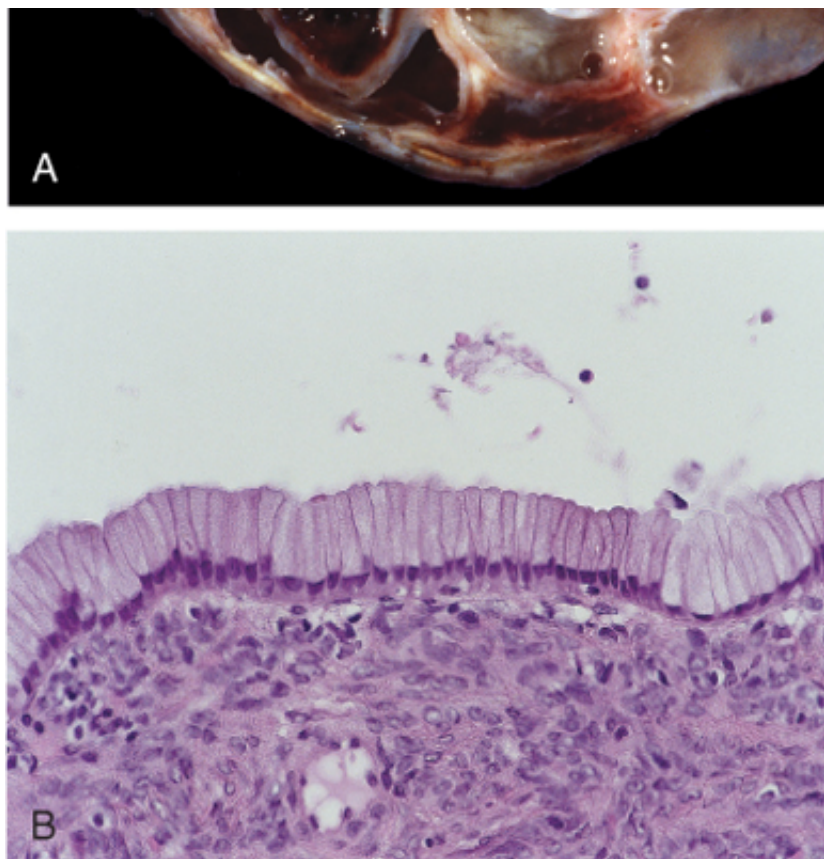
*Intraductal papillary mucinous neoplasms (IPMNs)* also produce cysts containing mucin, and can malignant. In contrast to mucinous cystic neoplasms, IPMNs arise more frequently in men than in head of the pancreas. IPMNs arise in the main pancreatic ducts and lack the cellular stroma seen 7).

### **Pancreatic Carcinoma**

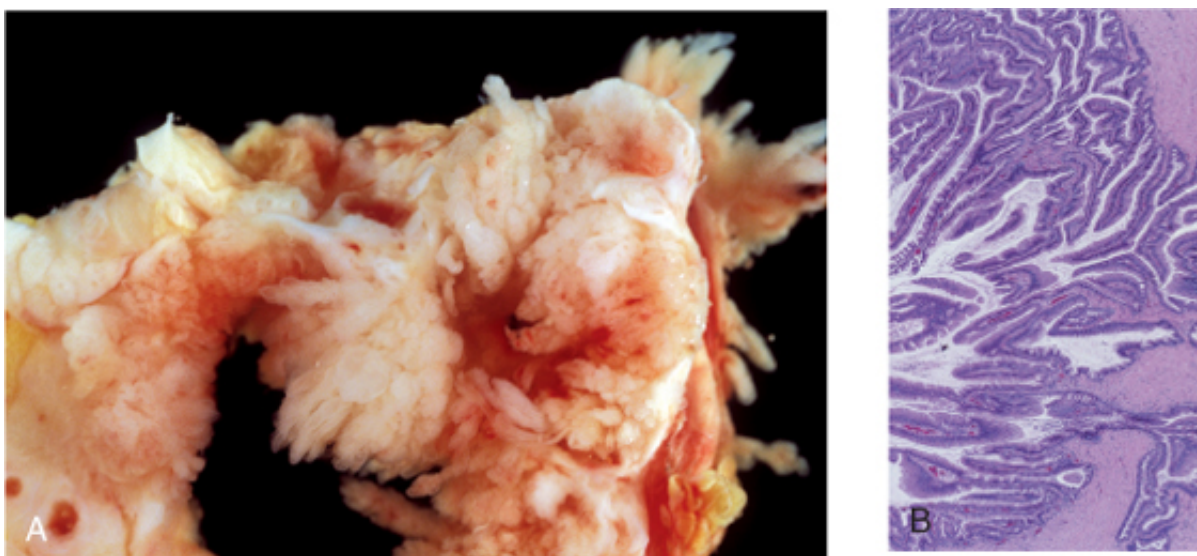
Pancreatic carcinoma is the fourth leading cause of cancer death in the United States, preceded c Although it is substantially less common than the other three malignancies, pancreatic carcinoma cancers because it has one of the highest mortality rates. Nearly 30,000 Americans are diagnosed virtually all will die of it; the 5-year survival rate is dismal-less than 5%.

### ***Pathogenesis***





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 Figure 17-6 Pancreatic mucinous cystadenoma. **A**, Cross-section through a mucinous multiloculated cyst in the tail of the pancreas, filled with tenacious mucin. **B**, The cysts are lined by columnar mucinous epithelium, with a densely cellular stroma.



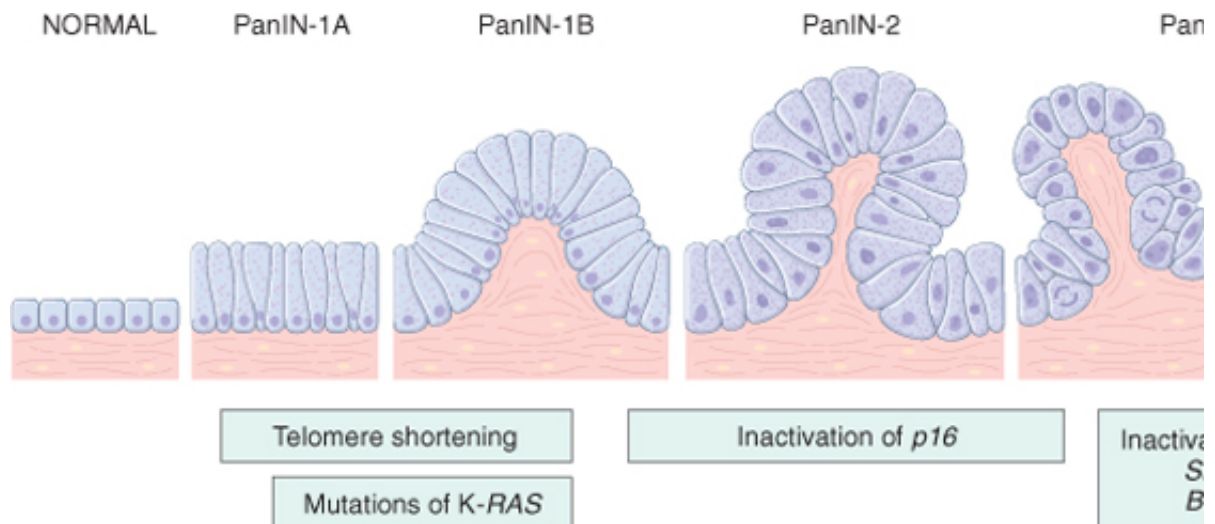
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 Figure 17-7 Intraductal papillary mucinous neoplasm. **A**, Cross-section through the head of the pancreas showing a dilated main pancreatic duct. **B**, The papillary mucinous neoplasm involved the main pancreatic duct (left) and is extending into the surrounding pancreatic tissue.

Like all cancers, pancreatic cancer is fundamentally a genetic disease arising as a consequence of

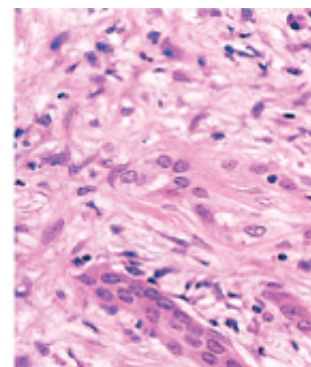


cancer-associated genes. In a pattern analogous to that seen in colon cancer (Chapter 6), there is changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive lesions in sm carcinoma (Fig. 17-8). Antecedent lesions are called "pancreatic intraepithelial neoplasias" (PanIN) relationship to frank malignancy includes the fact that they are often found adjacent to infiltrating c same genetic mutations. Moreover, the epithelial cells in PanINs show dramatic telomere shorteni to accumulating additional chromosomal abnormalities on their way to becoming invasive carcinoi alterations in pancreatic carcinogenesis affect *K-RAS*, *p16*, *SMAD4*, and *p53*:

The *K-RAS* gene is the most frequently altered oncogene in pancreatic cancer; it is activat cases. These mutations impair the intrinsic GTPase activity of the K-RAS protein so that it activates several intracellular signal transduction pathways culminating in the activation of *p16* (*CDKN2A*) gene is the most frequently inactivated tumor suppressor gene in pancreati cases. The p16 protein has a critical role in cell cycle control; inactivation removes an impc suppressor gene is inactivated in 55% of pancreatic cancers; it codes for a protein that play down-stream of the transforming growth factor- $\beta$  receptor. Its normal function is most likely apoptosis. Inactivation of the *p53* tumor suppressor gene occurs in 50% to 70% of pancrea both as a cell cycle checkpoint and as an inducer of apoptosis (Chapter 6).



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 Figure 17-8 Model for the development of pancreatic cancer. It is postulated that telomere shortening, and mutation inactivation of the *p16* tumor suppressor gene occurs at intermediate stages, and the inactivation of the *p53*, *SMAD4* at late stages. Note that while there is a general temporal sequence of changes, the accumulation of multiple mutations occurs in a specific order. (Adapted from Wilentz RE, et al.: Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia neoplastic progression. Cancer Res 60:2002, 2000.)





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Figure 17-9 Carcinoma of the pancreas. **A**, A cross-section through the head of the pancreas and adjacent common bile duct, showing the green discoloration of the duct resulting from total obstruction of bile flow and the green discoloration of the duct resulting from total obstruction of bile flow. **B**, Microscopic view of the tumor tissue, showing densely fibrotic (desmoplastic) stroma within the pancreatic substance.

What causes these molecular changes is unknown. It is primarily a disease of the elderly, with 80% occurring between 60 and 80. Carcinoma of the pancreas is more common in blacks than in whites. The strongest risk factor is smoking, which doubles the risk. Chronic pancreatitis and diabetes mellitus are also both associated with an increased risk. It is difficult to sort out whether chronic pancreatitis is the cause of pancreatic cancer or an effect of the cancer. Chronic pancreatitis can block the pancreatic duct and thereby produce chronic pancreatitis. A similar argument applies to diabetes and pancreatic cancer, since diabetes can occur as a consequence of pancreatic cancer. Familial cases are reported, and a growing number of inherited syndromes are now recognized that increase pancreatic cancer risk. For example, chronic pancreatitis (related to mutations in the *PRSS1* trypsinogen gene; see above) incurs a 50- to 80-fold increase in malignancy.

### Morphology

Approximately 60% of pancreatic cancers arise in the head of the gland, 15% in the body, and 25% in the tail. In 20%, the neoplasm diffusely involves the entire organ. Carcinomas of the pancreas are typically stellate, gray-white, poorly defined masses (Fig. 17-9A).

The vast majority of carcinomas are **ductal adenocarcinomas** recapitulating to some extent the normal duct epithelium by forming glands and secreting mucin. Two features are characteristic of ductal adenocarcinoma: it is highly invasive (even "early" invasive pancreatic cancers invade peripancreatic tissue), and it elicits an intense non-neoplastic host reaction composed of fibroblasts, lymphocytes, and inflammatory cells in the stroma (desmoplastic response).

Most carcinomas of the head of the pancreas obstruct the distal common bile duct. In 50% of such cases, there is marked distention of the biliary system, and patients typically exhibit jaundice. In marked contrast, **carcinomas of the body and tail of the pancreas do not impinge on the biliary tract and hence remain silent for some time. They may be widely disseminated by the time they are discovered.** Pancreatic cancers often invade the retroperitoneal space, entrapping adjacent nerves, and occasionally invade the spleen, transverse colon, and stomach. Peripancreatic, gastric, mesenteric, omentum, and lymph nodes are frequently involved, and the liver is often enlarged because of metastases. Metastases occur, principally to the lungs and bones.

Microscopically, pancreatic carcinoma is usually a **moderately to poorly differentiated adenocarcinoma** forming abortive tubular structures or cell clusters and exhibiting an aggressive growth pattern (Fig. 17-9B). Dense stromal fibrosis accompanies tumor invasion, and perineural invasion within and beyond the organ. Lymphatic invasion is also common.

Less common variants of pancreatic cancer include: **acinar cell carcinomas** show some differentiation with zymogen granules and exocrine enzyme production; **adenosquamous carcinomas** show focal squamous differentiation in addition to glandular differentiation; **undifferentiated carcinomas** lack glandular differentiation; and **osteoclast-like giant cells**.

### Clinical Features

*Carcinomas of the pancreas typically remain silent until their extension impinges on some other structure, but by that point these cancers are usually beyond cure. Obstructive jaundice can be associated with carcinomas of the head of the pancreas, but it rarely draws attention to the cancer soon enough. Weight loss, anorexia, and general debility are common in advanced disease. Migratory thrombophlebitis (Trousseau syndrome) occurs in about 10% of patients with pancreatic cancer.*



elaboration of platelet-aggregating factors and procoagulants from the tumor or its necrotic products.

The symptomatic course of pancreatic carcinoma is distressingly brief and progressive. Fewer than 10% are resectable at the time of diagnosis. There has long been a search for biochemical tests that could detect pancreatic cancers. Indeed, serum levels of many enzymes and antigens (e.g., carcinoembryonic and CA19-9) are neither specific nor sensitive enough to be used as screening tests. Several imaging techniques, including ultrasonography and CT, are helpful in diagnosis and performing percutaneous needle biopsy but

## SUMMARY

**Pancreatic Neoplasms** Pancreatic cancer probably arises from precursor lesions developing by a progressive accumulation of characteristic mutations of oncogenes and tumor suppressor genes (e.g., *p16*, *p53*, and *SMAD4*). Typically, they are diagnosed at a late stage with a dense stroma. Pancreatic cancer is usually only diagnosed after it is clinically apparent as an aggressive malignancy with a high mortality rate. Obstructive jaundice is a frequent complication if the head of the pancreas is involved.

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## 18 The Male Genital System\*

Disorders of the male genital system include a variety of malformations, inflammatory conditions, and neoplasms involving the penis and scrotum, prostate, and testes. In this chapter the major anatomic subdivisions of the male genital system are considered individually, because many of the diseases discussed tend to involve the various organs in a fairly selective fashion. The major exception to this anatomic grouping is the discussion of sexually transmitted diseases (STDs), which are described separately because of their frequent multisystem involvement. Because of many similarities in their presentations in both sexes, the manifestations of selected STDs in females are also considered in this chapter.





## PENIS

The penis may be affected by many congenital and acquired disorders. Only the most common malformations and neoplasms are considered here. Of the inflammatory disorders affecting the penis, a significant number are discussed later in the chapter.

### Malformations

The most common malformations of the penis include abnormalities in the location of the distal urethral orifice. *Hypospadias*, the more common of the two lesions, occurs in 1 in 250 live male births. The urethra lies along the ventral aspect of the penis. The urethral orifice, which may lie anywhere along the ventral aspect, is constricted, resulting in urinary tract obstruction and an increased risk of urinary tract infections. The other congenital anomalies, including inguinal hernias and undescended testes. The term *epispadias* refers to the urethral orifice on the dorsal aspect of the penis. Like hypospadias, epispadias may produce lower urinary tract dysfunction. A condition may result in urinary incontinence. Epispadias is commonly associated with *bladder extrophy*.

### Inflammatory Lesions

A significant number of inflammatory conditions of the penis are caused by STDs. Local inflammation also involves the penis. In addition, several other systemic inflammatory diseases may, on occasion, involve the penis.

The terms *balanitis* and *balanoposthitis* refer to local inflammation of the glans penis, or of the glans and prepuce, respectively. Most cases occur as a consequence of poor local hygiene in uncircumcised males, with accumulation of epithelial cells, sweat, and debris, termed *smegma*, acting as a local irritant. In such cases, the penis is tender; a purulent discharge may be present. *Phimosis* represents a condition in which the prepuce is too tight to retract over the glans penis. Although phimosis may occur as a congenital anomaly, most cases are acquired from previous episodes of balanoposthitis. Regardless of its origin, most cases of phimosis are accompanied by penile inflammation. When a stenotic prepuce is forcibly retracted over the glans penis, the result is a condition known as *paraphimosis*, with resultant congestion, swelling, and pain of the distal penis, a condition known as *paraphimosis* in severe cases.

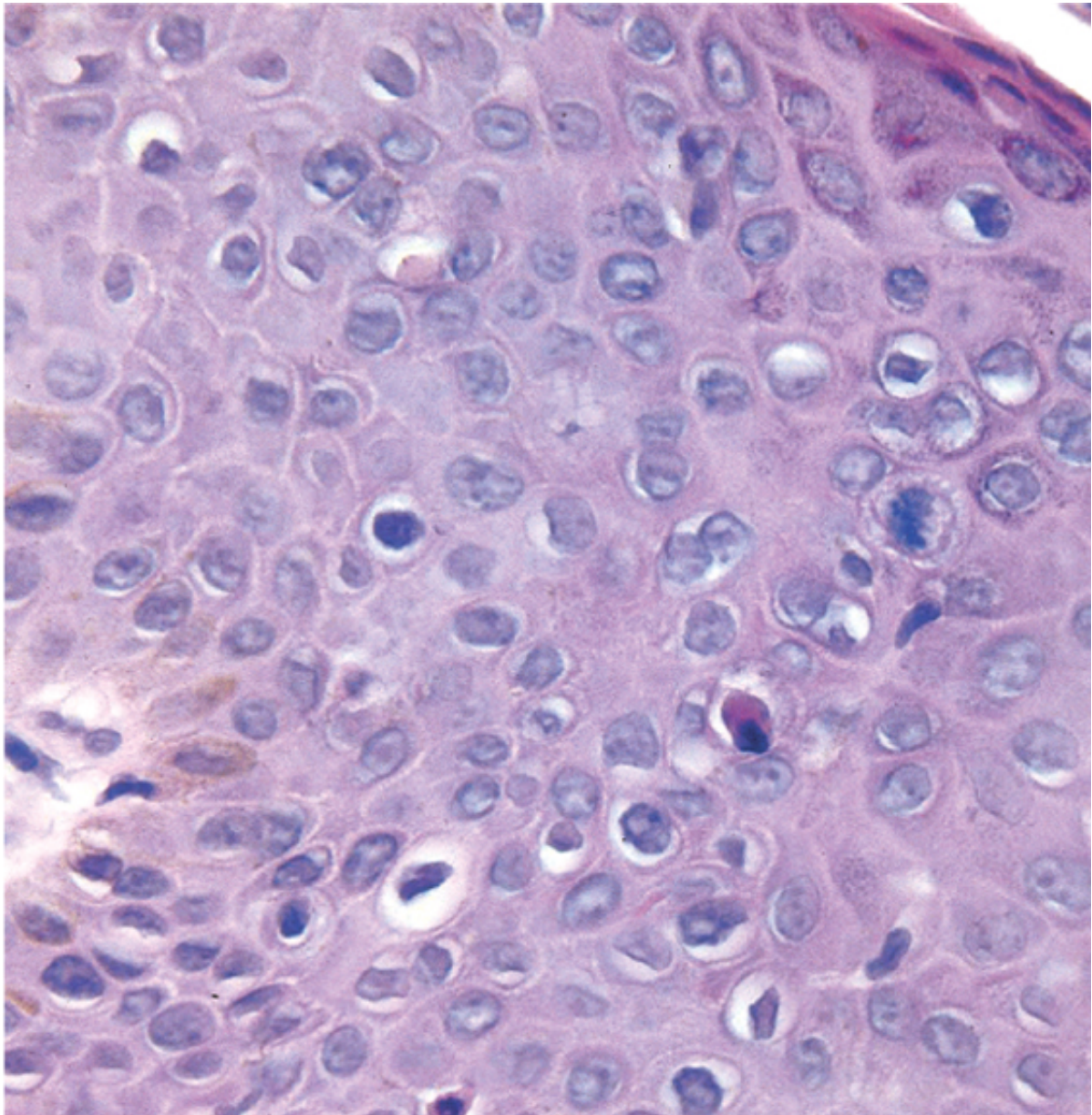
Fungi may infect the skin of the penis and scrotum, because growth of fungi is favored by warm, moist environments and poor hygiene. *Genital candidiasis* may occur in otherwise normal individuals, but it is particularly common in uncircumcised males. Candidiasis typically presents as an erosive, painful, intensely pruritic lesion involving the glans penis and the inner surface of the prepuce. Scrapings or biopsy specimens of the lesions reveal characteristic budding yeast forms and hyphae in the epidermis.

### Neoplasms

More than 95% of penile neoplasms originate from squamous epithelium. In the United States, squamous cell carcinoma of the penis is relatively uncommon, accounting for about 0.4% of all cancers in males. In developing countries, the rates are much higher. Most cases occur in uncircumcised patients older than 40 years of age. Several factors are associated with the pathogenesis of squamous cell carcinoma of the penis, including poor hygiene (with resultant exposure to smegma), smoking, and infection with human papillomavirus (HPV), particularly types 16 and 18.

As with squamous cell carcinomas at other sites, carcinomas of the penis are generally preceded by a premalignant stage, confined to the epidermis, termed *intraepithelial neoplasia* or *carcinoma in situ*. Three clinical variants of intraepithelial neoplasia, associated with HPV infection, occur on the penis. *Bowen disease* occurs in older uncircumcised males and presents as a plaque-like lesion on the shaft of the penis. Histologic examination reveals morphologically malignant cells with invasion of the underlying stroma (Fig. 18-1). Bowen disease is not unique to the penis but may also occur on mucosal surfaces, including the vulva and oral mucosa. Its major clinical importance lies in the possibility of progression to squamous cell carcinoma, a complication estimated to occur in as many as 33% of cases involving Bowen disease.

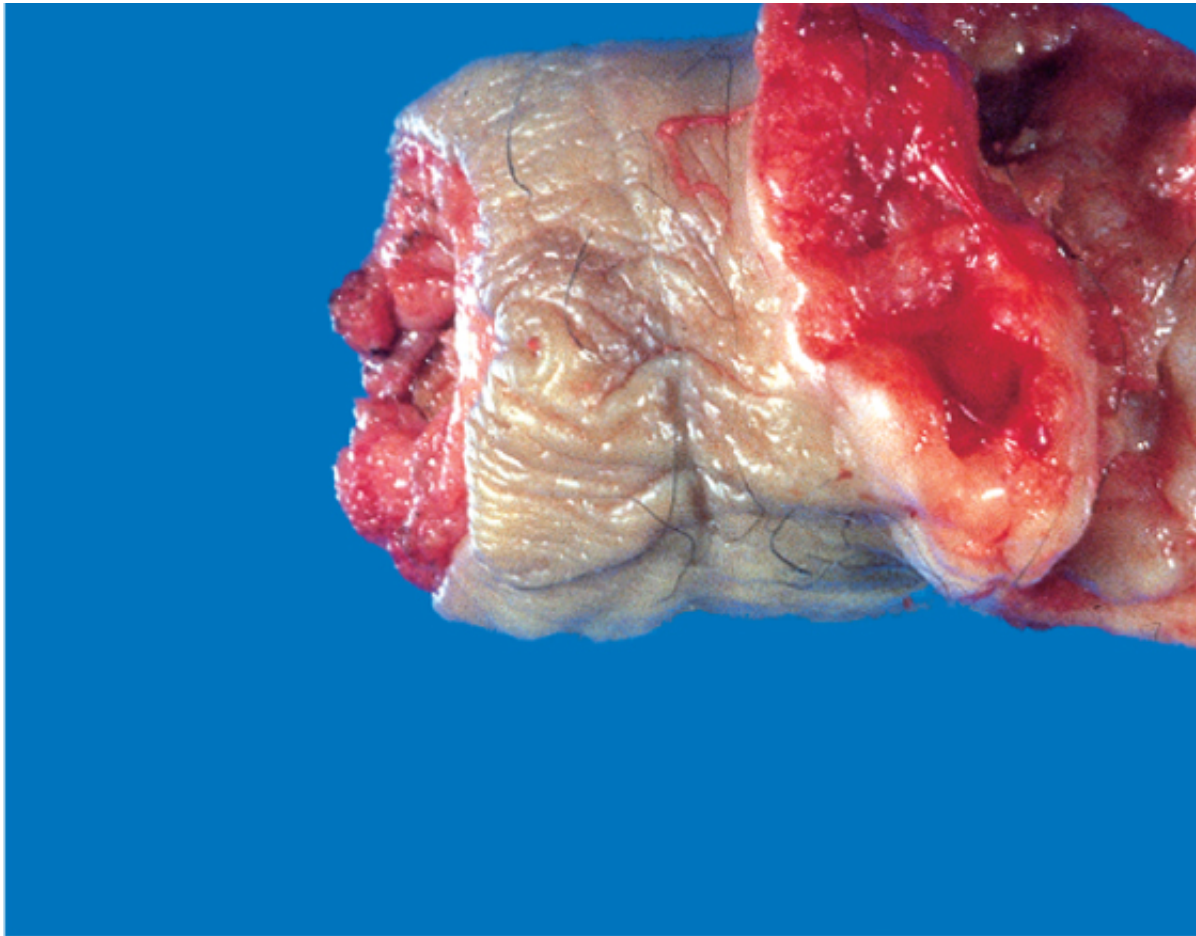
presents as an erythematous patch on the glans penis, it is called *erythroplasia of Queyrat*. Bowen disease is more common in older, sexually active males and is histologically identical to Bowen disease. Clinically, however, it presents with white patches on the glans and is most often transient, with only rare progression to carcinoma in immunocompetent patients.



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Figure 18-1 Bowen disease (carcinoma in situ) of the penis. The epithelium above the intact basement membrane consists of dysplastic, dyskeratotic epithelial cells with scattered mitoses above the basement membrane.







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 Figure 18-2 Carcinoma of the penis. The glans penis is deformed by a firm, ulcerated, and crusted mass.

*Squamous cell carcinoma* of the penis appears as a gray, crusted, papular lesion, most commonly on the glans. In advanced cases, the carcinoma infiltrates the underlying connective tissue to produce an indurated, ulcerated lesion (Figure 18-2). The histologic appearance is usually that of a keratinizing squamous cell carcinoma with infiltrative growth, similar to squamous carcinomas in other sites. *Verrucous carcinoma* is a variant of squamous cell carcinoma with a verrucous architecture, less striking cytologic atypia, and rounded, pushing deep margins. Most cases of squamous cell carcinoma are indolent, locally infiltrative lesions. Regional metastases are present in the inguinal lymph nodes at the time of diagnosis. Distant metastases are relatively uncommon. The overall 5-year survival rate at

## SUMMARY

### Neoplasms of the Penis

Squamous cell carcinoma and its precursor lesions are the most important neoplasms of the penis and are associated with HPV infection. Carcinoma in situ of the penis occurs in three forms: Bowenoid papulosis, and erythroplasia of Queyrat. Histologically they are similar to Bowenoid papulosis and erythroplasia of Queyrat. Squamous cell carcinoma occurs on the glans or shaft of the penis and is an ulcerated infiltrative lesion that may spread to inguinal nodes and infrequently to distant sites. Cases occur in uncircumcised males who are smokers.





## SCROTUM, TESTIS, AND EPIDIDYMISS

The skin of the scrotum may be affected by several inflammatory processes, including local fungal infections. Neoplasms of the scrotal sac are unusual. *Squamous cell carcinoma*, the most common of these, represents the first human malignancy associated with environmental influences, dating from Sir Percival Pott's discovery of the disease in chimney sweeps. Several disorders unrelated to the testes and epididymis cause scrotal enlargement. *Hydrocele*, the most common cause of scrotal enlargement, is an accumulation of serous fluid that may arise in response to neighboring infections or tumors, or it may be idiopathic. Accumulations of blood in the tunica vaginalis, termed *hematoceles* and *chyloceles*, respectively, may also cause testicular enlargement. In severe cases, obstruction, caused, for example, by filariasis, the scrotum and the lower extremities may enlarge and become edematous, termed *elephantiasis*.

The more important disorders of the scrotum involve the testes and their adnexal structures. Testicular disorders may be inflammatory, or neoplastic. They may manifest themselves in a variety of ways, including infertility. Distinguishing among many of these conditions, particularly those associated with testicular enlargement, by physical examination alone can be exceedingly difficult.

### Cryptorchidism and Testicular Atrophy

Cryptorchidism represents *failure of testicular descent* into the scrotum. Normally, the testes descend from the retroperitoneum into the scrotum by the third month of gestation and then through the inguinal canals into the scrotum during fetal development. In the newborn, diagnosis of cryptorchidism is difficult to establish with certainty before 1 year of age, particularly if the testis is not palpable. Testicular descent into the scrotum is not invariably present at birth. By 1 year of age, cryptorchidism is present in approximately 1% of the male population. Approximately 10% of these cases are bilateral. Several influences, including hormonal abnormalities, and mechanical problems (e.g., obstruction of the inguinal canal), may interfere with normal descent. Malpositioning of the gonad anywhere along its migration pathway. Additionally, cryptorchidism is associated with syndromes, such as the Prader-Willi syndrome ([Chapter 7](#)). In the vast majority of cases, however, the cause is unknown. Not surprisingly, bilateral cryptorchidism causes sterility. Unilateral cryptorchidism may be associated with a contralateral descended gonad and therefore may also lead to sterility. In addition to infertility, cryptorchidism is associated with a 5-fold increased risk of *testicular malignancy*. Individuals with unilateral cryptorchidism are also at risk for cancer in the contralateral, normally descended testis, suggesting that some intrinsic abnormality, perhaps in the undescended testis, may be responsible for the increased cancer risk. Surgical placement of the undescended testis into the scrotum at puberty decreases the likelihood of testicular atrophy and reduces, but does not eliminate, the risk of malignancy.

### Morphology

Cryptorchidism involves the right testis somewhat more commonly than the left. In unilateral cases, the condition is bilateral. The cryptorchid testis may be of normal size early in life, but a degree of atrophy is usually present by the time of puberty. Microscopic evidence of atrophy is evident by 5 to 6 years of age, and hyalinization is present by the time of puberty. It is usually accompanied by hyperplasia of Leydig cells. Foci of **intratubular germ cell neoplasia** may be present in cryptorchid testes and may be the source of subsequent tumors developing in the testis. Atrophic changes similar to those seen in cryptorchid testes may be caused by several conditions, including chronic ischemia, trauma, radiation, antineoplastic chemotherapy, and chronic elevation in estrogen levels (e.g., cirrhosis). Intratubular germ cell neoplasia is also seen in the latter conditions, however.

### SUMMARY

#### Cryptorchidism

Cryptorchidism refers to incomplete descent of the testis from the abdomen into the scrotum. It is present in about 1% of 1-year-old males. Bilateral or, in some cases, unilateral.

associated with tubular atrophy and sterility. The cryptorchid testis has a 3- to 10% risk of testicular cancer arising in foci of intratubular germ cell neoplasia within the testis. Orchiopexy reduces the risk of sterility and cancer.

## Inflammatory Lesions

Inflammatory lesions of the testis are more common in the epididymis than in the testis proper. Sexually transmitted diseases of the testis are associated with venereal disease and are discussed later in this chapter. These include nonspecific epididymitis and orchitis, mumps, and tuberculosis. *Nonspecific epididymitis* is a urinary tract infection with secondary ascending infection of the testis through the vas deferens or involved testis is typically swollen and tender and contains a predominantly neutrophilic inflammatory infiltrate. *Infection* in roughly 20% of infected adult males but rarely occurs in children. The affected testis is a predominantly lymphoplasmacytic inflammatory infiltrate. Severe cases may be associated with epithelium with resultant tubular atrophy, fibrosis, and sterility. Several conditions, including infectious granulomatous inflammatory reaction in the testis. Of these, *tuberculosis* is the most common. Testicular epididymitis, with secondary involvement of the testis. The histologic changes include granuloma formation, identical to that seen in active tuberculosis in other sites.

## Testicular Neoplasms

*Testicular neoplasms are the most important cause of firm, painless enlargement of the testis.* In the United States, about 100,000 males, with a peak incidence between the ages of 20 and 34 years. Tumors of the testis are composed of germ cell tumors and sex cord/stromal tumors. In adults, 95% of testicular neoplasms are malignant. Neoplasms derived from Sertoli or Leydig cells (sex cord/stromal tumors) are of non-germ cell origin, usually pursue a benign clinical course. The remainder of this section will focus on testicular germ cell tumors.

The cause of testicular neoplasms remains unknown. As noted previously, *cryptorchidism is associated with an increased risk of cancer* in the undescended testis, as well as an increased risk of cancer in the contralateral testis. Cryptorchidism is present in approximately 10% of cases of testicular cancer. Intersex syndromes, Klinefelter syndrome and gonadal dysgenesis, are also associated with an increased frequency of testicular neoplasms. A wide range of abnormalities in testicular germ cell neoplasms, the most common of which is an isochromosome of the Y chromosome (45,X). However, the role of these chromosomal aberrations in the pathogenesis of testicular neoplasms is increased in siblings of males with testicular cancers, although no consistent hereditary genetic pattern has been identified. The development of cancer in one testis is associated with a marked increase in the risk of cancer in the contralateral testis. Testicular tumors are more common in whites than in blacks, and the incidence has increased in both populations over recent decades.

## Classification and Histogenesis

**Table 18-1. Simplified Classification of Testicular Germ Cell Tumors**

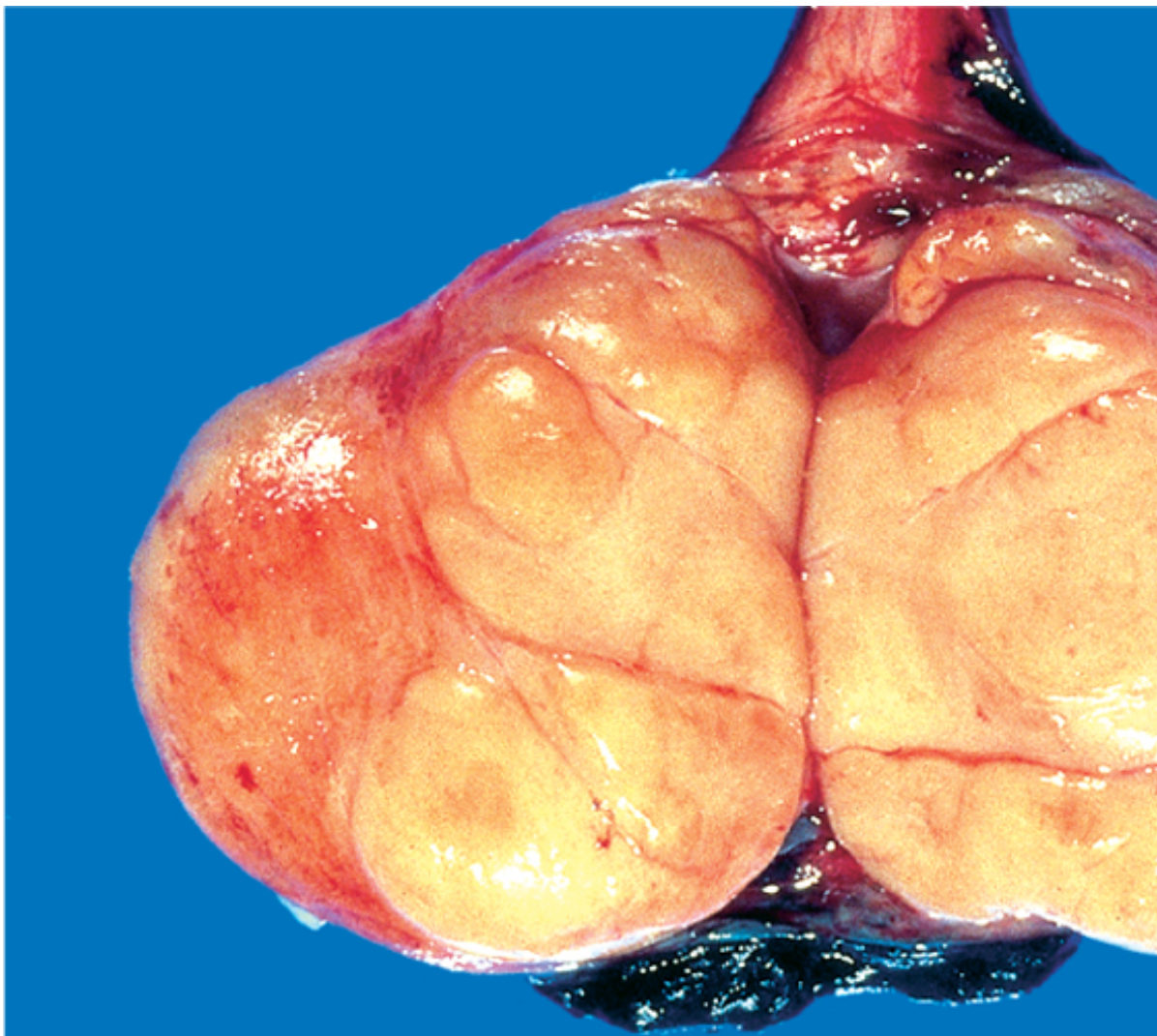
<b>Tumors with One Histologic Pattern</b>
Seminoma
* Embryonal carcinoma
*Yolk sac tumor
*Choriocarcinoma
*Teratomas
Mature
Immature
With malignant transformation of somatic elements
<b>Tumors with More Than One Histologic Pattern</b>

\*Together grouped as non-seminomatous tumors.

Several different classification schemes have been proposed for testicular neoplasms, based on the histologic pattern of the tumor.

Several different classification schemes have been proposed for testicular neoplasms, based on differing theories about their histogenesis. The World Health Organization classification is the most widely used (Table 18-1). In this schema, germ cell tumors of the testis are divided into two broad categories, seminoma (60% of cases) or nonseminoma (40% of cases). This classification is based on histologic pattern. Seminomas of the testis arise from primitive cells that may either differentiate along gonadal lines to produce embryonal germ cell tumors, giving rise to *nonseminomatous germ cell tumors*. Such totipotent cells may differentiate along extra-embryonic lines to form *yolk sac tumors*, or may differentiate along somatic cell lines to produce *teratomas*. This proposed histogenesis is supported by the histologic patterns among nonseminomatous germ cell tumors. The morphology of the more common seminoma is discussed in a separate section. The morphology of the more common nonseminomatous germ cell tumors is discussed in a separate section.

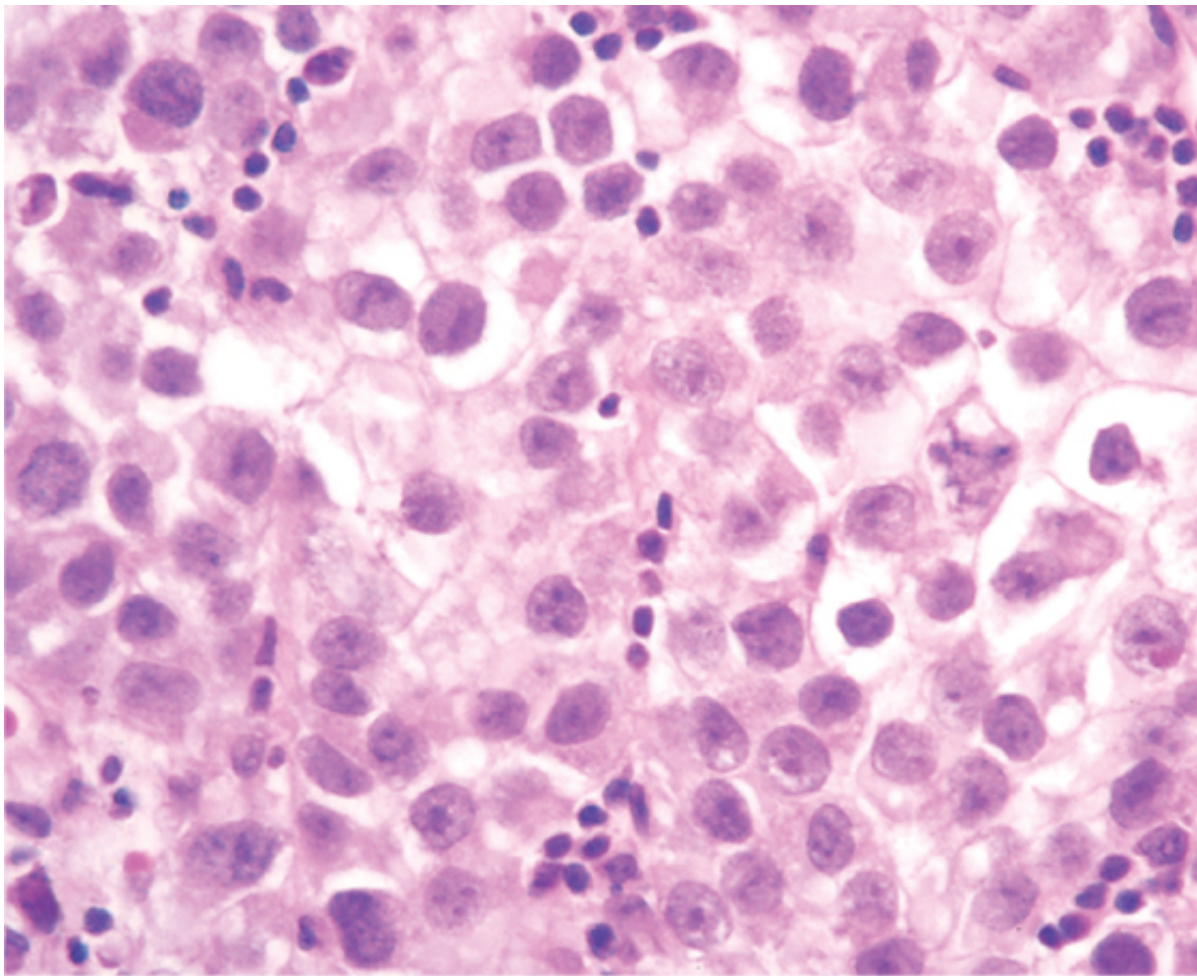
It is now widely believed that most testicular tumors arise from in situ lesions characterized as *intratubular germ cell neoplasia in situ* (IGCIS). IGCIS is present in conditions associated with a high risk of developing germ cell tumors (e.g., cryptorchidism). Foci of such in situ lesions are seen in testicular tissue adjacent to a testicular germ cell tumor in approximately 50% of cases.



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Figure 18-3 Seminoma of the testis appears as a fairly well circumscribed, pale, fleshy, and lobulated mass.







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Figure 18-4 Seminoma of the testis. Microscopic examination reveals large cells with distinct cell borders, pale nuclei, and a lymphocytic infiltrate.

### Morphology

**Seminomas**, sometimes referred to as "classic" seminomas to distinguish them from spermatocytic seminoma discussed below, account for about 50% of testicular germ cell tumors. They are histologically identical to ovarian dysgerminomas and to germinomas occurring in the central nervous system and other extra-gonadal sites. Seminomas are large, soft, well-demarcated gray-white tumors that bulge from the cut surface of the affected testis (Fig. 18-3). They are typically confined to the testis by an intact tunica albuginea. Large tumors may contain areas of necrosis, usually without hemorrhage. The presence of hemorrhage should prompt a search for an associated nonseminomatous germ cell component to the tumor. Microscopically, seminomas are composed of **large, uniform cells with distinct cell borders, clear, glycogen-rich cytoplasm, and conspicuous nucleoli** (Fig. 18-4). The cells are often arrayed in small lobules separated by thin fibrous septa. A lymphocytic infiltrate is usually present and may, on occasion, overshadow the tumor. A granulomatous inflammatory reaction may also be present. In as many as 25% of cases, immunohistochemical staining positively for human chorionic gonadotropin (hCG) can be seen. Some of these hCG-positive cells are morphologically similar to syncytiotrophoblasts, and they are presumably the source of the hCG. High hCG concentrations that may be encountered in some males with pure seminoma.

Another, less common, morphologic variant of seminoma is the so-called **spermatocytic seminoma**, which tends to occur in older patients than do classic seminomas. Spermatocytic seminomas contain a mixture of large uninucleate or multinucleate tumor cells, and small cells with round nuclei, resembling secondary spermatocytes. There is no association with intratubular germ cell neoplasia.

exceedingly rare, in contrast to the behavior of classic seminoma.

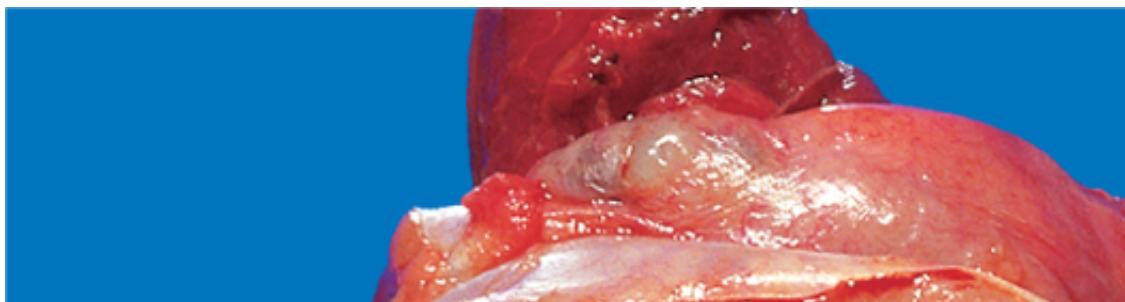
**Embryonal carcinomas** are ill-defined, invasive masses containing foci of hemorrhage (Fig. 18-5). The primary lesions may be small, even in patients with systemic metastases that invade the epididymis and spermatic cord. The constituent cells are **large and primitive, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli**. Cells may be arrayed in undifferentiated, solid sheets or may contain glandular structures or papillae (Fig. 18-6). In most cases, other patterns of germ cell neoplasia (e.g., yolk sac tumor or choriocarcinoma) are admixed with the embryonal areas. Pure embryonal carcinoma is rare among all testicular germ cell tumors. As with other germ cell tumors of the testes, foci of dysplasia or neoplasia are frequently present in the adjacent seminiferous tubules.

**Yolk sac tumors**, also termed **endodermal sinus tumors**, are the most common malignant germ cell neoplasm in children younger than 3 years of age. In adults, yolk sac tumors are rare and are often associated with embryonal carcinoma. In the histogenetic scheme noted previously, yolk sac tumor represents **endodermal sinus** differentiation of totipotential neoplastic cells. Grossly, these tumors may be well demarcated. Histologic examination discloses low cuboidal to columnar cells forming microcysts, sheets, glands, and papillae, often associated with eosinophilic hyaline material. A distinctive feature is the presence of structures resembling primitive glomeruli, the **Schwimmer bodies**.  $\alpha$ -fetoprotein (AFP) can be demonstrated within the cytoplasm of the neoplastic cells using immunohistochemical techniques.

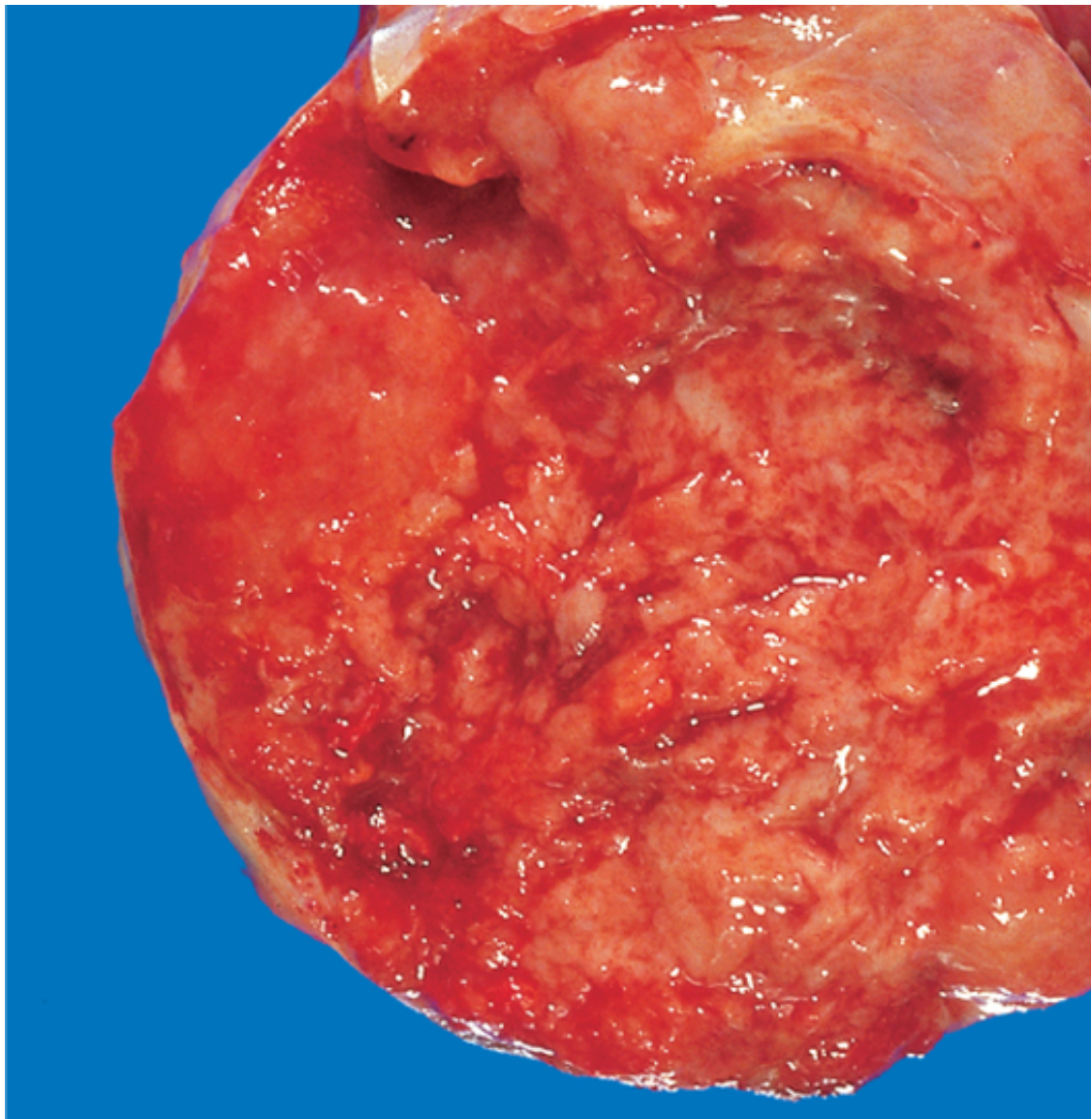
**Choriocarcinomas** represent differentiation of pluripotential neoplastic germ cells. Grossly, the primary tumors are often small, nonpalpable lesions, even with extensive hemorrhage. Microscopically, choriocarcinomas are composed of sheets of small cuboidal cells, some with or capped by large, eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei. These represent **cytotrophoblastic** and **syncytiotrophoblastic** differentiation, respectively. Fetal or placental villi are not seen. The hormone hCG can be identified with appropriate immunohistochemical staining, particularly within the cytoplasm of the syncytiotrophoblastic cells.

**Teratomas** represent differentiation of neoplastic germ cells along **somatic** cell lines. They are firm masses that on cut surface often contain cysts and recognizable areas of cartilage, bone, or other mature tissue. Two major variants of pure teratoma are recognized. **Mature teratomas** contain fully differentiated tissues from one or more germ cell layers (e.g., neural tissue, cartilage, adipose tissue, bone, etc.) and are benign (Fig. 18-9). **Immature teratomas**, in contrast, contain immature somatic elements and are malignant. **Teratomas with somatic-type malignancies** are characterized by the development of frank malignancy in preexisting teratomatous elements, usually in the form of squamous cell carcinoma or adenocarcinoma. Pure teratomas in prepubertal males are usually benign, but in adults they often metastasize in as many as 37% of cases. As with other germ cell tumors, adult testicular teratomas often contain other malignant germ cell elements and therefore should be regarded as malignant neoplasms.

**Mixed germ cell tumors**, as noted, account for approximately 40% of all testicular tumors. Combinations of any of the described patterns may occur in mixed tumors, the most common being a combination of teratoma, embryonal carcinoma, and yolk sac tumors.



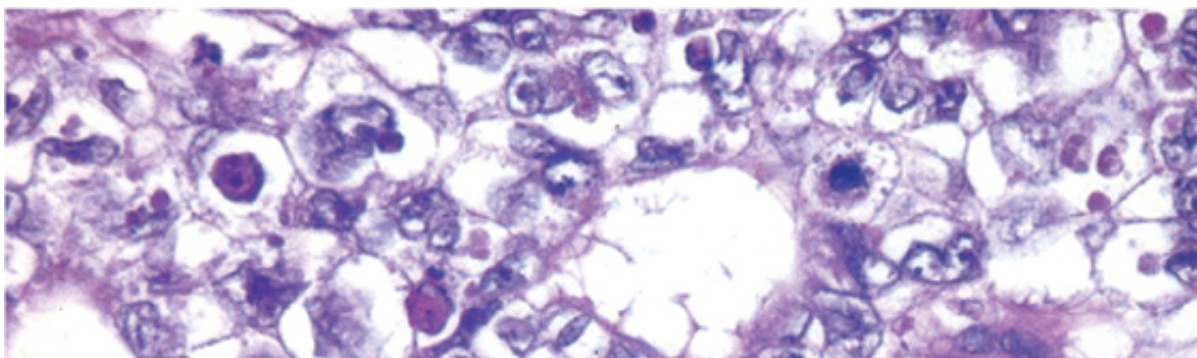




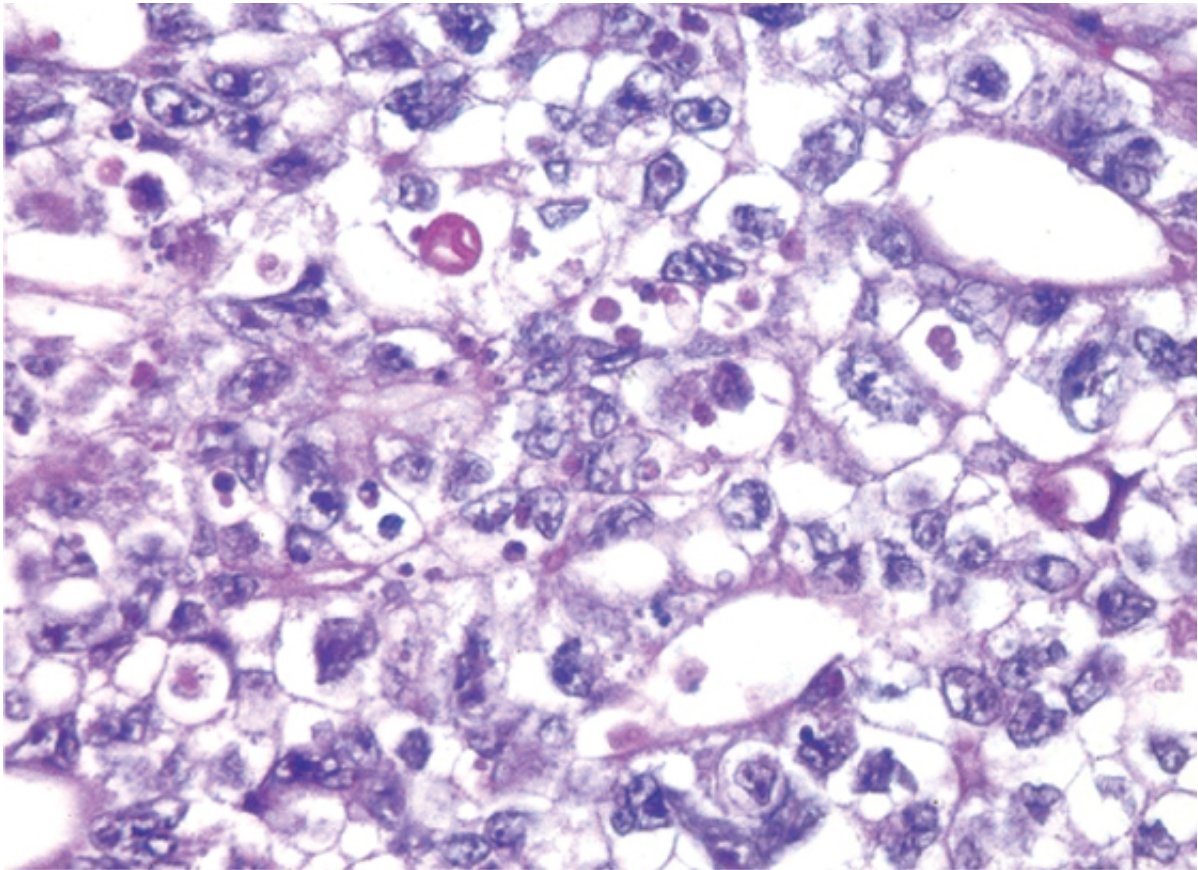
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Figure 18-5 Embryonal carcinoma. In contrast to the seminoma illustrated in Figure 18-3, the embryonal

### *Clinical Features*

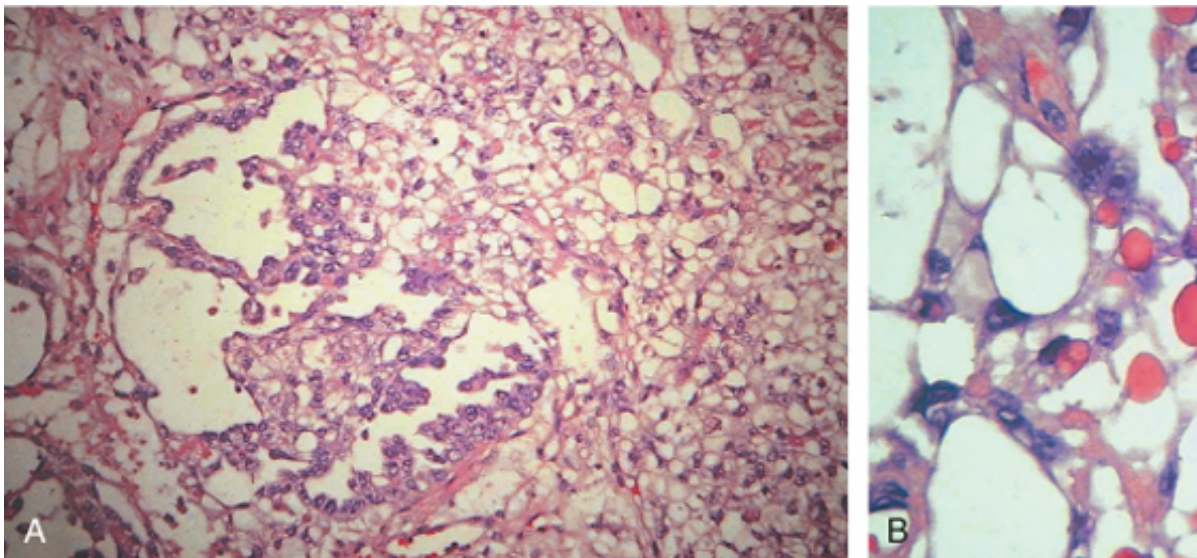
Clinically, it is best to consider testicular germ cell tumors under two broad categories: Seminoma. As be evident from the discussion that follows, these two groups of tumors have somewhat distinctive





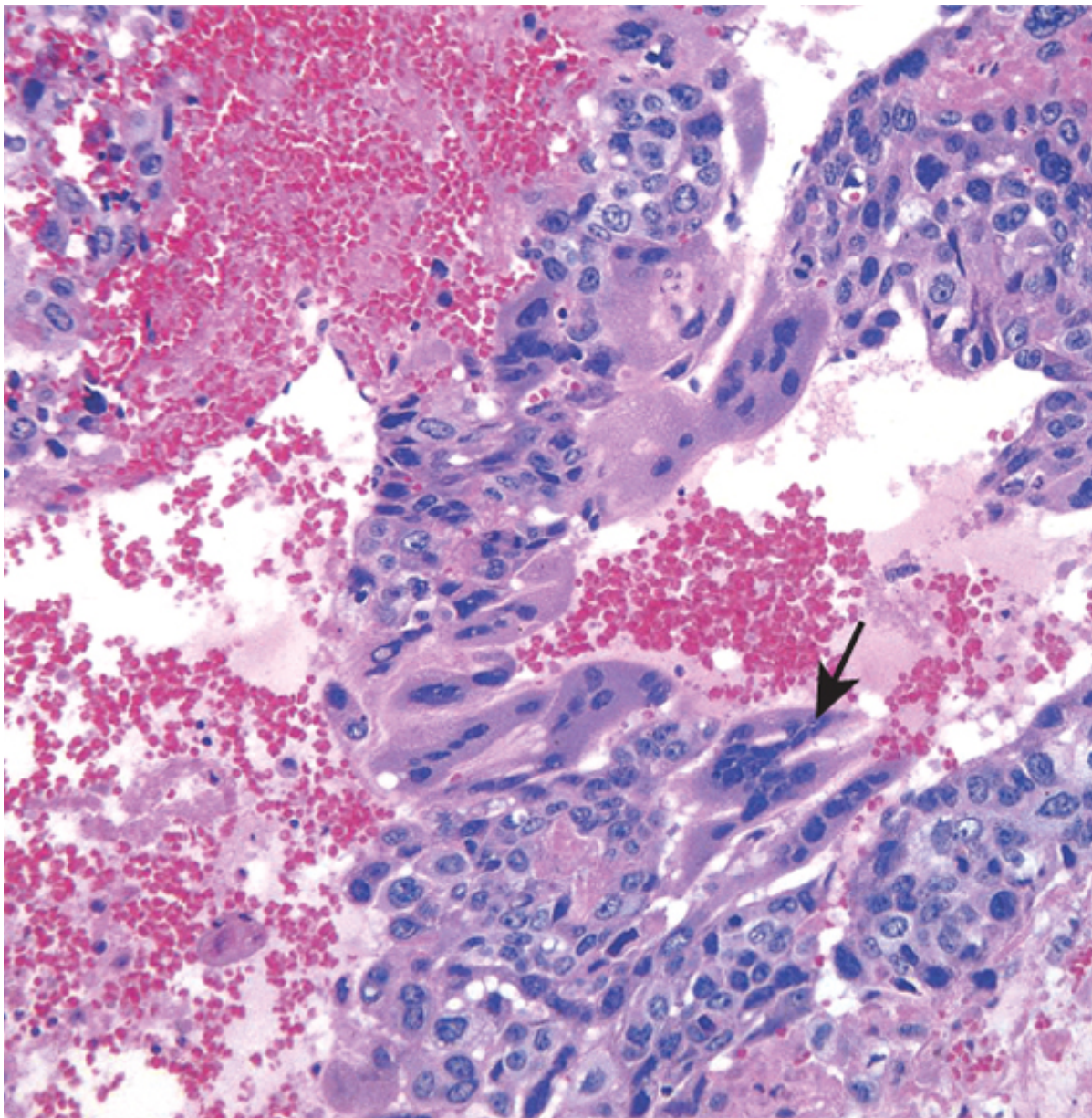


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 Figure 18-6 Embryonal carcinoma shows sheets of undifferentiated cells as well as primitive glandular differentiation.



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 Figure 18-7 Yolk sac carcinoma. **A**, Low-power photomicrograph demonstrating areas of loosely textured, microcystic developing glomerulus. **B**, Higher power photomicrograph demonstrating characteristic hyaline droplets within the tumor cells.





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 Figure 18-8 Choriocarcinoma shows cytotrophoblastic cells with central nuclei (arrowhead, upper right) and syncytiotrophoblastic cells embedded in eosinophilic cytoplasm (arrow, middle). Hemorrhage and necrosis

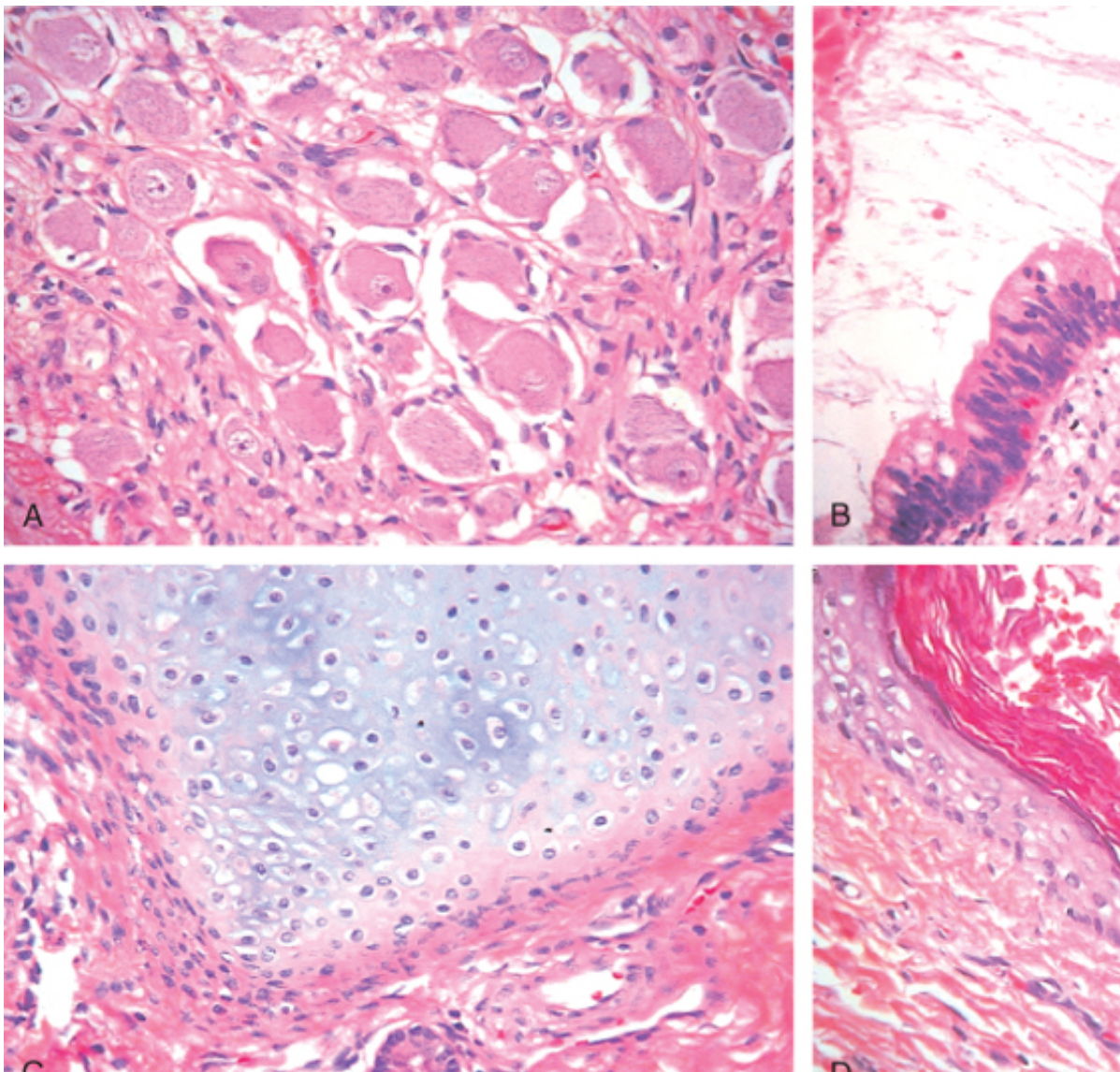
Individuals with testicular germ cell neoplasms present most frequently with *painless enlargement* especially nonseminomatous germ cell neoplasms, may have widespread metastases at diagnosis. *Seminomas often remain confined to the testis* for prolonged intervals and may reach cons. Metastases are most commonly encountered in the iliac and para-aortic lymph nodes, particularly Hematogenous metastases occur later. In contrast, *nonseminomatous germ cell neoplasms tend* and hematogenous routes. Hematogenous metastases are most common in the liver and lungs. Metastases are histologically identical to the primary testicular tumor; rarely they may contain other germ cell elements staged as follows:

Stage I: Tumor confined to the testis  
 Stage II: Regional lymph node metastases only  
 Stage III: Distant organ metastases



Assay of *tumor markers* secreted by tumor cells is important in the clinical evaluation and staging. hCG, produced by neoplastic syncytiotrophoblastic cells, is always elevated in patients with choriocarcinoma. Seminoma, including syncytiotrophoblastic cells without cytotrophoblastic cells, may also contain syncytiotrophoblastic cells without cytotrophoblastic cells. Approximately 10% to 25% of seminomas elaborate hCG. AFP is a glycoprotein normally synthesized by several other fetal tissues. Nonseminomatous germ cell tumors containing elements of yolk sac (endodermal) contrast to hCG, the presence of AFP is a reliable indicator of the presence of a nonseminomatous germ cell tumor because yolk sac elements are not found in pure seminomas. Because mixed patterns are common, elevations of both hCG and AFP. In addition to their role in the primary diagnosis and staging of testicular tumors, determinations of hCG and AFP are useful for monitoring patients for persistent or recurrent tumor. However, that AFP is also elevated in hepatocellular carcinoma ([Chapter 16](#)).

The treatment of testicular germ cell neoplasms is considered a success story of chemotherapy. Although testicular cancer occurs in the United States yearly, fewer than 400 men are expected to die of the disease. In 1986, Lance Armstrong won the Tour de France bicycle race a record seven times! The prognosis of the tumor and the stage of disease at the time of diagnosis. Seminomas are common and respond well to chemotherapy. The prognosis of many nonseminomatous germ cell tumors has improved with the use of platinum-based chemotherapy regimens.





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Figure 18-9 Teratoma. Testicular teratomas contain mature cells from endodermal, mesodermal, and ectodermal germ layers. The same tumor containing (A) neural (ectodermal), (B) glandular (endodermal), (C) cartilaginous (mesodermal) tissue.

**Table 18-2. Summary of Testicular Tumors**

<b>Tumor</b>	<b>Peak Age (yr)</b>	<b>Morphology</b>
Seminoma	40-50	Sheets of uniform polygonal cells with cleared cytoplasm; lymphocytes in the interstitium
Embryonal carcinoma	20-30	Poorly differentiated, pleomorphic cells in cords, sheets, or papillary formations; may contain some yolk sac and choriocarcinoma cells
Yolk sac tumor	3	Poorly differentiated endothelium-like, cuboidal, or columnar cells
Choriocarcinoma (pure)	20-30	Cytotrophoblast and syncytiotrophoblast without villus formation
Teratoma	All ages	Tissues from all three germ-cell layers with varying degrees of differentiation
Mixed tumor	15-30	Variable, depending on mixture; commonly teratoma and embryonal carcinoma

AFP,  $\alpha$ -fetoprotein; hCG, human chorionic gonadotropin.

## SUMMARY

### Testicular Tumors

Testicular tumors are the most common cause of painless testicular enlargement. The frequency of testicular tumors has increased in undescended testis and in males with gonadal dysgenesis. About 95% of testicular tumors arise from germ cells, and the remainder arise from Sertoli or Leydig cells. Germ cell tumors may be composed of one histologic pattern (60% of cases) or mixed (40%). The most common single histologic pattern is seminoma, followed by embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. Mixed germ cell tumors contain more than one element, most commonly embryonal carcinoma, teratoma, and yolk sac tumor. Clinically testicular tumors can be divided into two groups: seminomatous and nonseminomatous. Seminomas remain confined to the testis for a long time and spread to lymph nodes—rarely to distant sites. Nonseminomatous tumors tend to spread early to lymph nodes and blood vessels. hCG is produced by syncytiotrophoblasts and is always elevated in nonseminomatous tumors. AFP is made by yolk sac endoderm and is elevated in yolk sac tumors. Most nonseminomatous tumors have mixed patterns of histology and produce both hCG and AFP.





## PROSTATE

The most important categories of prostatic disease are inflammatory lesions (prostatitis), nodular hyperplasia, and prostatic adenocarcinoma.

### Prostatitis

Prostatitis may be acute or chronic. The classification of prostatitis is based on a combination of clinical features, histologic findings, and, in selected cases, culture of fractionated urine specimens obtained before and after prostatic massage. Acute prostatitis is caused by the same organisms associated with other acute urinary tract infections, particularly *Escherichia coli* and other gram-negative rods. Most patients with acute prostatitis have concomitant infection of the urethra and urinary bladder. In some cases, organisms may reach the prostate by direct extension from the urethra or urinary bladder. Chronic prostatitis may follow clinical episodes of acute prostatitis, or may develop insidiously. In some cases of chronic prostatitis, bacteria similar to those responsible for acute bacterial prostatitis are designated as *chronic bacterial prostatitis*. In other instances the presence of an increased number of leukocytes in the prostatic secretions attests to prostatic inflammation, but bacteriologic findings are negative. Such cases, termed *chronic abacterial prostatitis*, account for most cases of chronic prostatitis. Several nonbacterial agents implicated in the pathogenesis of chronic abacterial prostatitis, including *Chlamydia trachomatis* and *Ureaplasma urealyticum*, can also cause chronic abacterial prostatitis.

#### Morphology

**Acute prostatitis** is characterized by the presence of an acute, neutrophilic inflammatory infiltrate, glandular congestion, and stromal edema. Neutrophils are initially most conspicuous within the glandular spaces. As the infection progresses, the inflammatory infiltrate destroys glandular epithelium and invades the surrounding stroma, resulting in the formation of microabscesses. Grossly visible as a red, swollen prostate, acute prostatitis can develop with extensive tissue destruction, e.g. in diabetic patients.

The histologic features of **chronic prostatitis** are nonspecific in most cases and include a mixed inflammatory infiltrate, lymphoid infiltrate, evidence of glandular injury, and, frequently, concomitant acute inflammation. Evidence of tissue destruction and fibroblastic proliferation, along with the presence of inflammatory cells, such as neutrophils, is required for a histologic diagnosis of chronic prostatitis.

A morphologic variant of chronic prostatitis, **granulomatous prostatitis**, deserves special mention. Granulomatous prostatitis is not a single disease but is instead a morphologic reaction to various insults. Granulomatous inflammation may be encountered with systemic inflammatory diseases such as disseminated tuberculosis, sarcoidosis, fungal infections, Wegener granulomatosis, and as a nonspecific reaction to inspissated prostatic secretions and after transurethral resection of the prostate. The morphologic features of granulomatous prostatitis include multinucleate giant cells, eosinophils, and foamy histiocytes, sometimes accompanied by eosinophils. Caseous necrosis is characteristic of tuberculous prostatitis. It is not seen in other forms of granulomatous prostatitis.

### Clinical Features

The clinical manifestations of prostatitis include *dysuria*, *urinary frequency*, *lower back pain*, and *perineal discomfort*. The prostate may be enlarged and tender, particularly in acute prostatitis, in which local symptoms are more prominent. Leukocytosis. Chronic prostatitis, even if asymptomatic, may serve as a reservoir for organisms causing recurrent urinary tract infections. Chronic bacterial prostatitis, therefore, is one of the most important causes of recurrent urinary tract infections.

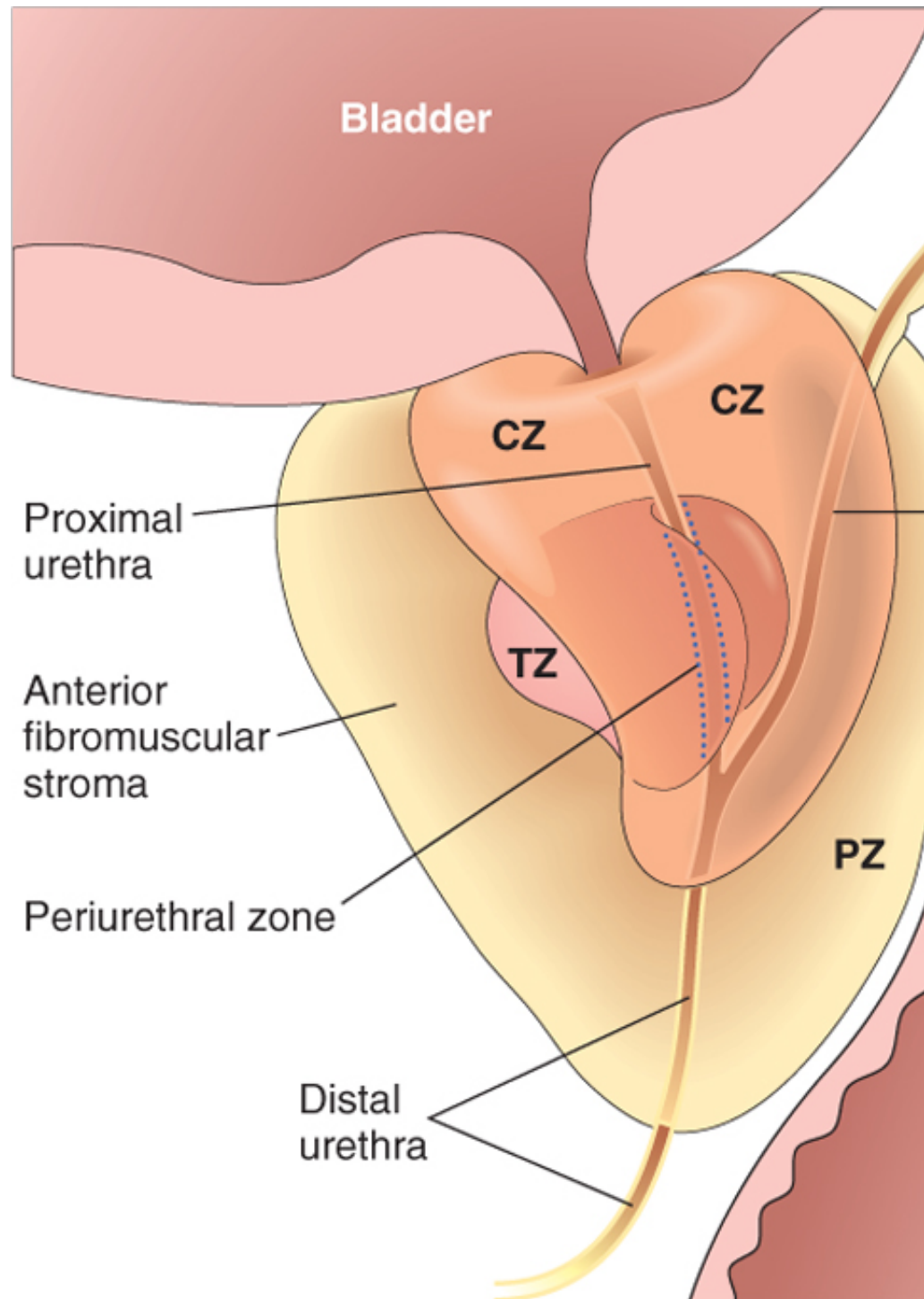
### SUMMARY Prostatitis

Prostatitis may be acute or chronic and the latter may be bacterial or abacterial. Acute prostatitis is caused by *E. coli* and other gram-negative rods that cause urinary tract infections. Chronic bacterial prostatitis is caused by the same organisms and may follow an acute episode insidiously. Chronic abacterial prostatitis is caused by *C. trachomatis* and *U. urealyticum*.



acute prostatitis causes dysuria, frequency, and low back pain. Chronic pro: symptomatic or silent. It is an important cause of recurrent urinary tract infe

### Nodular Hyperplasia of the Prostate



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Figure 18-10 Adult prostate. The normal prostate contains several distinct regions, including a central zone (CZ), and a periurethral zone. Most carcinomas arise from the peripheral glands of the organ and are often palpable di  
hynernlasia in contrast arises from more centrally situated glands and is more likely to produce urinary obstr

hyperplasia, in contrast, arises from more centrally situated glands and is more likely to produce urinary obstruction.

The normal prostate consists of glandular and stromal elements surrounding the urethra. The prostate is divided into several biologically distinct regions, the most important of which are the peripheral, central, transitional, and anterior fibromuscular. The types of proliferative lesions are different in each region. For example, most *hyperplastic* lesions arise in the central and transitional zones of the prostate, while most *carcinomas* (70% to 80%) arise in the peripheral zones.

*Nodular hyperplasia*, also termed *glandular* and *stromal hyperplasia*, is an extremely common abnormality affecting a significant number of men by the age of 40, and its frequency rises progressively with age, reaching 90% by age 70. Nodular hyperplasia is characterized by proliferation of both stromal and epithelial elements, with resultant enlargement of the prostate. In severe cases, urinary obstruction. "Benign prostatic hypertrophy" (BPH), a time-honored synonym for nodular hyperplasia, is now considered redundant and a misnomer, because all hypertrophies are benign and the fundamental lesion is a hyperplasia.

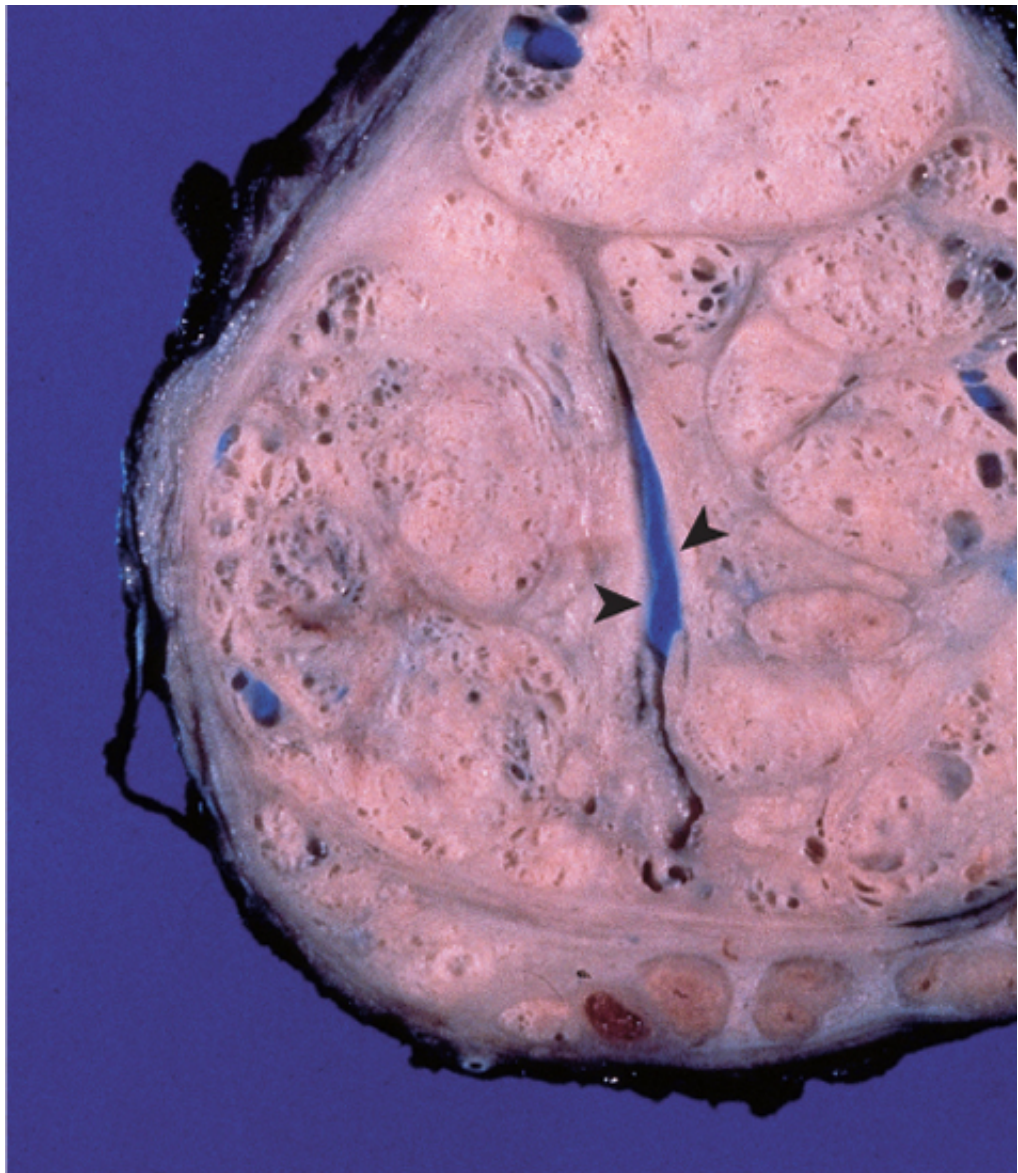
Although the cause of nodular hyperplasia remains incompletely understood, it is clear that *androgen* plays a major role in its *development*. Nodular hyperplasia does not occur in males castrated before the onset of puberty or in those treated with drugs that block androgen activity. Dihydrotestosterone (DHT), an androgen derived from *testosterone*<sup>®</sup> through the action of 5 $\alpha$ -reductase, and its metabolite, 3 $\alpha$ -androstane-20-one, seem to be major hormonal stimuli for stromal and glandular proliferation. DHT binds to nuclear androgen receptors and, in turn, stimulates synthesis of DNA, RNA, and protein, leading to hyperplasia. This forms the basis for the current use of 5 $\alpha$ -reductase inhibitors in the treatment of nodular hyperplasia. Because no study has shown a conclusive association between circulating androgen levels and nodular hyperplasia, it follows that local, intraprostatic concentrations of androgens and androgen receptors are more important in the condition. Experimental work has also identified age-related increases in estrogen levels that may play a role in the condition. Estrogen receptors on prostatic parenchymal cells, thereby functioning in the pathogenesis of nodular hyperplasia.

### Morphology

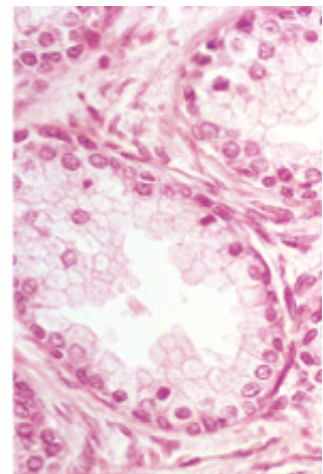
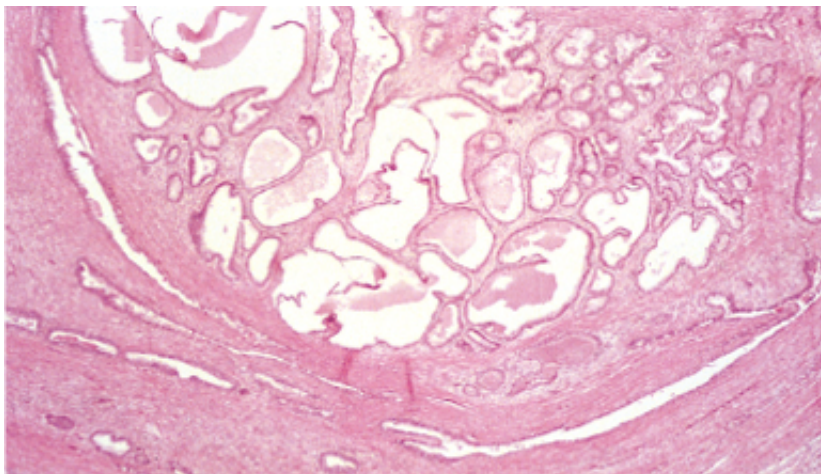
As noted, nodular hyperplasia arises most commonly in the inner, periurethral glands, particularly from those that lie above the verumontanum. The affected prostate is enlarged, with the weight in excess of 300 gm reported in severe cases. The cut surface contains many fairly well-circumscribed nodules that bulge from the cut surface (Fig. 18-11). This nodularity may be present throughout the prostate, but is **usually most pronounced in the inner (central and transitional) region**. The nodules may have a lobular appearance or may contain cystic spaces, the latter corresponding to dilated glandular lumina. In histologic sections, the urethra is usually compressed by the hyperplastic nodules. In some cases, hyperplastic glandular and stromal elements lying just under the epithelium of the prostatic urethra may project into the bladder lumen as a pedunculated mass, resulting in urethral obstruction.

Microscopically the hyperplastic nodules are composed of varying proportions of proliferating glandular elements and fibromuscular stroma. The hyperplastic glands are lined by tall, columnar epithelium with a prominent peripheral layer of flattened basal cells; crowding of the proliferating epithelium results in the formation of papillary projections in some glands (Fig. 18-12). The glandular lumina often contain proteinaceous secretory material, termed **corpora amylacea**. The glands are surrounded by a layer of stromal elements. Other nodules are composed predominantly of spindle-shaped cells in a dense, fibromuscular connective tissue. Areas of infarction are fairly common in advanced cases of nodular hyperplasia, frequently accompanied by foci of squamous metaplasia in adjacent glands.





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 Figure 18-11 Nodular prostatic hyperplasia. Well-defined nodules compress the urethra (arrowheads).







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Figure 18-12 Nodular hyperplasia. **A**, Low-power photomicrograph demonstrates a well-demarcated nodule at the edge of the section. In other cases of nodular hyperplasia, the nodularity is caused predominantly by stromal, rather than glandular, proliferation. **B**, Higher magnification view demonstrates the morphology of the hyperplastic glands, with the characteristic dual cell population: the inner columnar cell layer.

### Clinical Features

Clinical manifestations of prostatic hyperplasia occur in only about 10% of men with the disease. It preferentially involves the inner portions of the prostate, its most common manifestations are those that include difficulty in starting the stream of urine (hesitancy) and intermittent interruption of the urine. In severe cases, it can develop complete urinary obstruction, with resultant painful distention of the bladder and, if neglected, can lead to renal failure. Symptoms of obstruction are frequently accompanied by urinary urgency, frequency, and nocturia. A combination of residual urine in the bladder and chronic obstruction increases the risk of urinary tract infections.

## SUMMARY

### Nodular Hyperplasia of the Prostate

Nodular hyperplasia of prostate is characterized by benign proliferation of stromal and glandular elements. DHT, an androgen derived from testosterone<sup>Rx</sup>, is the major hormone that promotes proliferation. Nodular hyperplasia most commonly affects the inner periurethral region of the prostate, and the nodules compress the prostatic urethra. Microscopically the nodules are composed of stroma and glands. Hyperplastic glands are lined by two cell layers: an inner layer composed of columnar cells and an outer layer composed of flattened basal cells. Clinical symptoms are seen in men older than 50 years of age and include hesitancy, urgency, nocturia, and poor urinary stream. Chronic recurrent urinary tract infections. Acute urinary obstruction may occur.

### Carcinoma of the Prostate

Carcinoma of the prostate is the most common visceral cancer in males, ranking as the second most common cause of cancer deaths in men older than 50 years of age, after carcinoma of the lung. It is predominantly a disease of men between the ages of 65 and 75 years. Latent cancers of the prostate are even more common than overt cancers, with an overall frequency of more than 50% in men older than 80 years of age.

Although the cause of carcinoma of the prostate remains unknown, clinical and experimental observations suggest that both heredity and environment all have a role in its pathogenesis. Cancer of the prostate does not develop in men who have had a prostatectomy, suggesting that *androgens* probably contribute to its development. A hormonal influence is further suggested by the fact that many carcinomas of the prostate can be inhibited by orchiectomy or by the administration of estrogen. In a case of nodular hyperplasia of the prostate, however, the function of hormones in the pathogenesis remains poorly understood.

*Hereditary* contributions have also been implicated in light of the increased risk of disease among men with a family history of prostate cancer. Symptomatic carcinoma of the prostate is more common and occurs at an earlier age in African Americans, Asians, or Hispanics. Whether such racial differences occur as a consequence of genetic influences or as a result of a combination of the two remains unknown. However, the frequency of *incidental* prostatic cancers found at autopsy is similar in all races, suggesting that race figures more importantly in the growth of established lesions than in the initial development of the disease. On finding prostate cancer genes, but no definitive data are available. In studies of familial cases, several genes have been identified. In sporadic cases, hypermethylation of glutathione S-transferase p1 (*GSTP1*) on chromosome 11, and telomere shortening are relatively common genetic alterations. Recent studies have identified several family transcription factors in the pathogenesis of prostate cancer. Recall that these transcription factors are also found in sarcoma. Interestingly, racial variations in the number of CAG repeats in the androgen receptor gene have been associated with the incidence of prostate cancer in African Americans. Perhaps these polymorphisms influence the ac-



A possible role for *environmental influences* is suggested by the increased frequency of prostatic and by significant geographic differences in the incidence of the disease. Carcinoma of the prostate is common in the United States and relatively uncommon in Japan and certain other Asian countries. Males emigrating from these countries to the United States have a lower risk of prostate cancer; the risk of disease is intermediate in subsequent generations, in keeping with the development of this disease. Among environmental influences, a diet high in animal fat has been



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Figure 18-13 Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect (*lower left*). Note the spongy appearance of the benign peripheral zone on the contralateral side.

### Morphology

**Seventy to eighty percent of prostate cancers arise in the outer (peripheral) zone.** The cancer is palpable as irregular hard nodules by rectal digital examination. Because of the slow growth, the cancer is less likely to cause urethral obstruction in its initial stages than is nodular hyperplasia. The cancer typically appears as ill-defined masses just beneath the capsule of the prostate. On gross examination, carcinoma appears as firm, gray-white to yellow lesions that infiltrate the adjacent glandular tissue (Fig. 18-13). Metastases to regional pelvic lymph nodes may occur early. The cancer often infiltrates the seminal vesicles and periurethral zones of the prostate and may

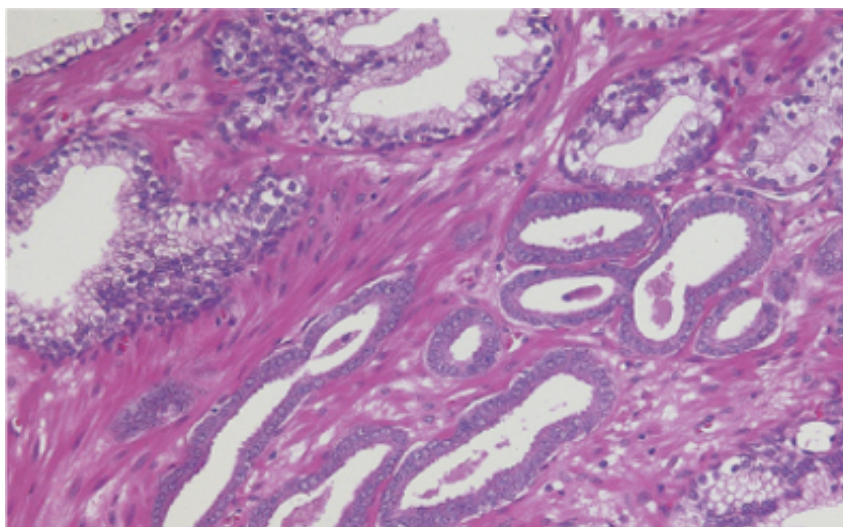
tissues and the wall of the urinary bladder. Denonvilliers fascia, the connective tissue layer separating the lower genitourinary structures from the rectum, usually prevents growth of the tumor into the rectum; therefore, invasion of the rectum is less common than is invasion of other contiguous structures.

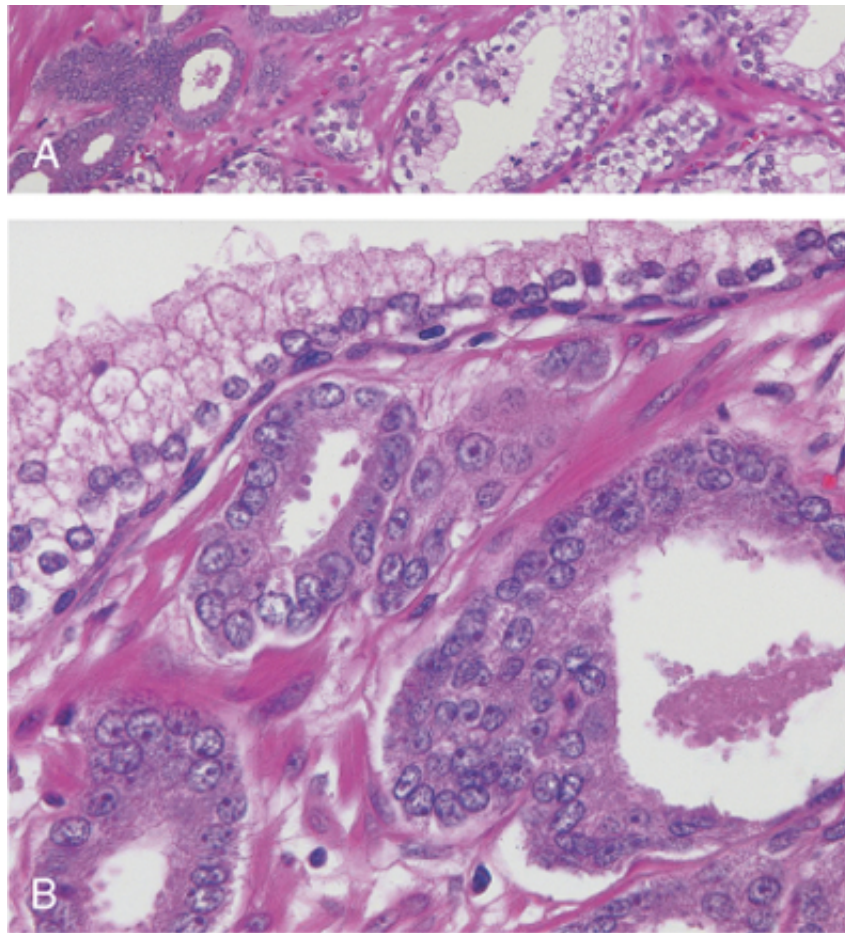
Microscopically, most prostatic carcinomas are **adenocarcinomas** exhibiting variable degrees of differentiation. The better differentiated lesions are composed of small glands that infiltrate the stroma in an irregular, haphazard fashion. In contrast to normal and hyperplastic prostatic glands, carcinomas lie "back to back" and appear to dissect sharply through the native stroma. The neoplastic glands are lined by a single layer of cuboidal cells with conspicuous nuclei. The prominent nucleoli seen in normal or hyperplastic glands is absent. With increasing degrees of anaplasia, the glands lose their glandular structures, papillary or cribriform epithelial structures, and, in extreme cases, the cellular differentiation. Cells with pleomorphic, hyperchromatic nuclei are present. Glands adjacent to areas of invasive carcinoma often contain foci of epithelial atypia, or **prostatic intraepithelial neoplasia (PIN)**. Because of its association with infiltrating carcinoma, PIN has been suggested as a probable precursor to carcinoma. PIN has been subdivided into high-grade and low-grade patterns, depending on the degree of atypia. Importantly, high-grade PIN shares molecular changes with invasive carcinoma, leading to the argument that PIN is an intermediate between normal and frankly malignant tissue.

A number of histologic grading schemes have been proposed for carcinoma of the prostate, based on features such as the degree of glandular differentiation, the architecture of the glands, the degree of anaplasia, and mitotic activity. A commonly used method for grading is the **Gleason** system. Despite the potential difficulties associated with incomplete sampling in biopsy material and the subjectivity of histologic evaluation, Gleason grade has proved to correlate reasonably well with the extent of prostatic carcinoma (discussed later) and the prognosis.

### *Clinical Features*

Carcinomas of the prostate are often clinically silent, particularly during their early stages. Approximately 10% are discovered unexpectedly, during histologic examination of prostate tissue removed for nodular hyperplasia. The incidence approaches 30% in men between 30 and 40 years of age. Because most cancers begin in the peripheral zone, they may be discovered during routine digital rectal examination. More extensive disease may present as "prostatism," including local discomfort and evidence of lower urinary tract obstruction similar to that seen in benign hyperplasia. Physical examination in such cases typically reveals evidence of locally advanced disease. More aggressive carcinomas of the prostate may first come to clinical attention because of bone pain. Regrettably, this is not an uncommon mode of presentation. Bone metastases, particularly to the osteolytic type, cause either osteolytic (destructive) or, more commonly, osteoblastic (bone-producing) lesions. *The finding of bone metastases in an older male is strongly suggestive of advanced prostatic carcinoma.*





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Figure 18-14 **A**, Photomicrograph of a small focus of adenocarcinoma of the prostate demonstrating small gland. Higher magnification shows several small malignant glands with enlarged nuclei, prominent nucleoli, and dark cytoplasm (top).

Assay of serum levels of *prostate-specific antigen* (PSA) has gained widespread use in the diagnosis of prostate cancer. PSA is a serine proteolytic enzyme produced by both normal and neoplastic prostatic epithelium. PSA is secreted into the prostatic ducts and thence into seminal fluid, where it increases sperm motility by maintaining seminal secretions. A PSA level of 4.0 ng/L has been used as the upper limit of normal. Cancer cells produce more PSA than normal prostatic epithelium. PSA levels of 4.0 ng/L or higher are indicative of prostate cancer. However, there is an overlap in serum levels exists between the two conditions. Moreover, in a minority of cases of cancer confined to the prostate, serum PSA is not elevated. Because of these problems with both specificity and sensitivity, PSA is not used as an isolated screening test for cancer of the prostate. Its diagnostic value is enhanced when used in conjunction with other procedures, such as digital rectal examination, transrectal sonography, and biopsy. Although serum PSA levels tend to be higher in men with carcinomas than in those with benign prostatic hyperplasia, a limitations as a diagnostic screening test, serum PSA concentration is of great value in monitoring the response to therapy. PSA levels greater than 10 ng/L indicate a higher risk for recurrence of cancer, with rising levels after ablative therapy indicative of recurrence and/or the development of metastatic disease. Testing of PSA values may further enhance its diagnostic utility. These include rate of change of PSA, determination of the ratio between the serum PSA value and volume of the prostate gland (PSA density), and determination of the ratio between the serum PSA value and volume of the prostate gland (PSA density). Free PSA levels greater than 25% indicate a lower risk for recurrence of cancer. Such refinements are likely to be most useful when PSA levels are between 4 and 10 ng/L.

**Table 18-3. Staging of Prostatic Adenocarcinoma Using the TNM System**

**TNM**



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## Designation Anatomic Findings

### Extent of Primary Tumor (T)

<b>T1</b>	<b>CLINICALLY INAPPARENT LESION (BY PALPATION/IMAGING STUDIES)</b>
T1a	Involvement of ≤5% of resected tissue
T1b	Involvement of >5% of resected tissue
T1c	Carcinoma present on needle biopsy (following elevated PSA)
<b>T2</b>	<b>PALPABLE OR VISIBLE CANCER CONFINED TO PROSTATE</b>
T2a	Involvement of ≤50% of one lobe
T2b	Involvement of >50% of one lobe, but unilateral
T2c	Involvement of both lobes
<b>T3</b>	<b>LOCAL EXTRAPROSTATIC EXTENSION</b>
T3a	Extracapsular extension
T3b	Seminal vesical invasion
<b>T4</b>	<b>INVASION OF CONTIGUOUS ORGANS AND/OR SUPPORTING STRUCTURES INCLUDING EXTERNAL SPHINCTER, LEVATOR MUSCLES, OR PELVIC FLOOR</b>
<b>Status of Regional Lymph Nodes (N)</b>	
<b>N0</b>	<b>NO REGIONAL NODAL METASTASES</b>
<b>N1</b>	<b>METASTASIS IN REGIONAL LYMPH NODES</b>
<b>Distant Metastases (M)</b>	
<b>M0</b>	<b>NO DISTANT METASTASES</b>
<b>M1</b>	<b>DISTANT METASTASES PRESENT</b>
M1a	Metastases to distant lymph nodes
M1b	Bone metastases
M1c	Other distant sites

PSA, prostate-specific antigen.

*Anatomic staging* of the extent of disease has an important role in the evaluation and treatment of Prostate cancer is staged by clinical examination, surgical exploration, radiographic imaging techniques, histologic grade of the tumor and levels of tumor markers. The anatomic extent of disease and the histologic grade for prostate cancer and correlate well with prognosis. Carcinoma of the prostate is treated with various therapies, and hormonal manipulations. Localized disease is usually treated with surgery, external-beam radiation therapy. Hormonal therapy has a central role in the treatment of advanced carcinomas. Androgens are androgen sensitive and are inhibited to some degree by androgen ablation. Surgical or pharmacologic androgen receptor-blocking agents have all been used to control the growth of disseminated lesions. Serial measurement of PSA is noted, is useful to monitor patients for recurrent or progressive disease. The prognosis for patients with stage T1 or T2 lesions is good, with more than 90% of patients surviving 10 years or longer. The outlook for patients with stage T3 or T4 lesions remains poor, with 10-year survival rates in this group ranging from 10% to 40%.

## SUMMARY

### Carcinoma of the Prostate

Carcinoma of the prostate is a common cancer of older men between 65 and 75 years of age. It is more common in American blacks than in Caucasians. Carcinomas of the prostate are commonly found in the outer, peripheral glands and may be palpable by rectal examination. They are adenocarcinomas with variable differentiation and anaplasia. Neoplastic cells are arranged in single layer of cells. Grading of prostate cancer by the Gleason system correlates with prognosis. Most localized cancers are clinically silent and are detected by elevated PSA concentrations in older men. Advanced cancers present with metastases to lymph nodes and bones. Serum PSA concentrations under 4 ng/mL are considered normal, and PSA levels above 4 ng/mL are suggestive of prostate cancer. PSA levels may also be elevated above 4 ng/mL in conditions such as nodular hyperplasia and prostatitis, hence biopsy is required for diagnosis. Evaluation of PSA concentrations after treatment has great value in monitoring response to therapy.



recurrent disease.



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## SEXUALLY TRANSMITTED DISEASES (STDs)

**Table 18-4. Classification of Important Sexually Transmitted Diseases**

Pathogens	Disease or Syndrome and Population Principles		
	Males	Both	Females
<b>Viruses</b>			
Herpes simplex virus		Primary and recurrent herpes, neonatal herpes	
Hepatitis B virus		Hepatitis	
Human papillomavirus	Cancer of penis (some cases)	Condyloma acuminatum	Cervical dysplasia and
Human immunodeficiency virus		Acquired immunodeficiency syndrome	
<b>Chlamydiae</b>			
<i>Chlamydia trachomatis</i>	Urethritis, epididymitis, proctitis	Lymphogranuloma venereum	Urethral syndrome, sequelae
<b>Mycoplasmas</b>			
<i>Ureaplasma urealyticum</i>	Urethritis		Cervicitis
<b>Bacteria</b>			
<i>Neisseria gonorrhoeae</i>	Epididymitis, prostatitis, urethral stricture	Urethritis, proctitis, pharyngitis, disseminated gonococcal infection	Cervicitis, endometritis (infertility, ectopic preg
<i>Treponema pallidum</i>		Syphilis	
<i>Haemophilus ducreyi</i>		Chancroid	
<i>Calymmatobacterium granulomatis</i>		Granuloma inguinale (donovanosis)	
<i>Shigella</i> sp.	Enterocolitis*		
<i>Campylobacter</i> sp.	Enterocolitis*		
<b>Protozoa</b>			
<i>Trichomonas vaginalis</i>	Urethritis, balanitis	Vaginitis	
<i>Entamoeba histolytica</i>	Amebiasis*		
<i>Giardia lamblia</i>	Giardiasis*		

\*Most important in homosexual populations.

Modified and updated from Krieger JN: Biology of sexually transmitted diseases. Urol Clin North Am 11:15, 1984.

STDs have complicated human existence for centuries and continue to do so at the present time. cases of STD occur every year, and of these, 4 million affect 15- to 19-year-olds and 6 million affect infectious diseases that require notification of the Centers for Disease Control in the United States include chlamydia, gonorrhea, acquired immunodeficiency syndrome (AIDS), syphilis, and hepatitis common STDs are genital herpes and genital HPV infection, but these do not require notification. immunodeficiency virus (HIV) infection, HPV, hepatitis B, and infection with *E. histolytica*, are discussed here focus on some of the more important of these entities that are not conveniently addressed in

### Syphilis

... ..

Syphilis, or lues, is a chronic venereal infection caused by the spirochete *Treponema pallidum*. From the sixteenth-century Europe as the Great Pox, syphilis has remained an endemic infection in all parts of the world. Approximately 6000 cases are reported every year, and this number has been on an upward trajectory with a disparity, with African Americans affected 30 times more often than whites.

*T. pallidum* is a fastidious spirochete whose only natural hosts are humans. The usual source of infection is a mucosal lesion in a sexual partner in the early (primary or secondary) stages of syphilis. The organism is transmitted during sexual intercourse across minute breaks in the skin or mucous membranes of the uninfected partner. *T. pallidum* is transmitted across the placenta from mother to fetus, particularly during the early stages of infection. Once introduced into the body, the organisms are rapidly disseminated to distant sites by lymphatics and the blood. The appearance of lesions at the primary inoculation site. Between 9 and 90 days (a mean of 21 days) after infection, a lesion, termed a *chancre*, appears at the point of entry. Systemic dissemination of organisms continues as the immune response mounts. Two types of antibodies are formed: nontreponemal antibodies and treponemal antibodies. As discussed in detail later, detection of these antibodies plays an important part in the diagnosis of syphilis. However, immunity, however, fails to eradicate spirochetes introduced during the primary inoculation.

The chancre of primary syphilis resolves spontaneously over a period of 4 to 6 weeks and is followed by the development of *secondary syphilis*. The manifestations of secondary syphilis, including skin lesions, generalized lymphadenopathy and variable mucocutaneous lesions and reflect the presence of organisms in the body during the primary phase of the disease. *The mucocutaneous lesions of both primary and secondary syphilis are highly infectious*. Like the chancre, the lesions of secondary syphilis resolve spontaneously. At this point patients are said to be in *early latent phase syphilis*. Mucocutaneous lesions may recur. The US Public Health Service has restricted the definition of early latent syphilis to the period 1 year after the onset of secondary syphilis.

Patients with untreated syphilis then enter into an asymptomatic, *late latent* phase of the illness. In this phase, late symptomatic lesions may develop over the next 5 to 20 years. This late symptomatic phase, or *tertiary syphilis*, is characterized by the development of lesions in the cardiovascular system, central nervous system, or, less frequently, in other organs. It is difficult to demonstrate during the later stages of disease, and patients with late latent or tertiary syphilis are more infectious than are those in the primary or secondary stages of disease.

Syphilis is common in HIV-infected patients. Like all other ulcerative genital diseases, syphilis promotes the progression of HIV infection.

### **Morphology**

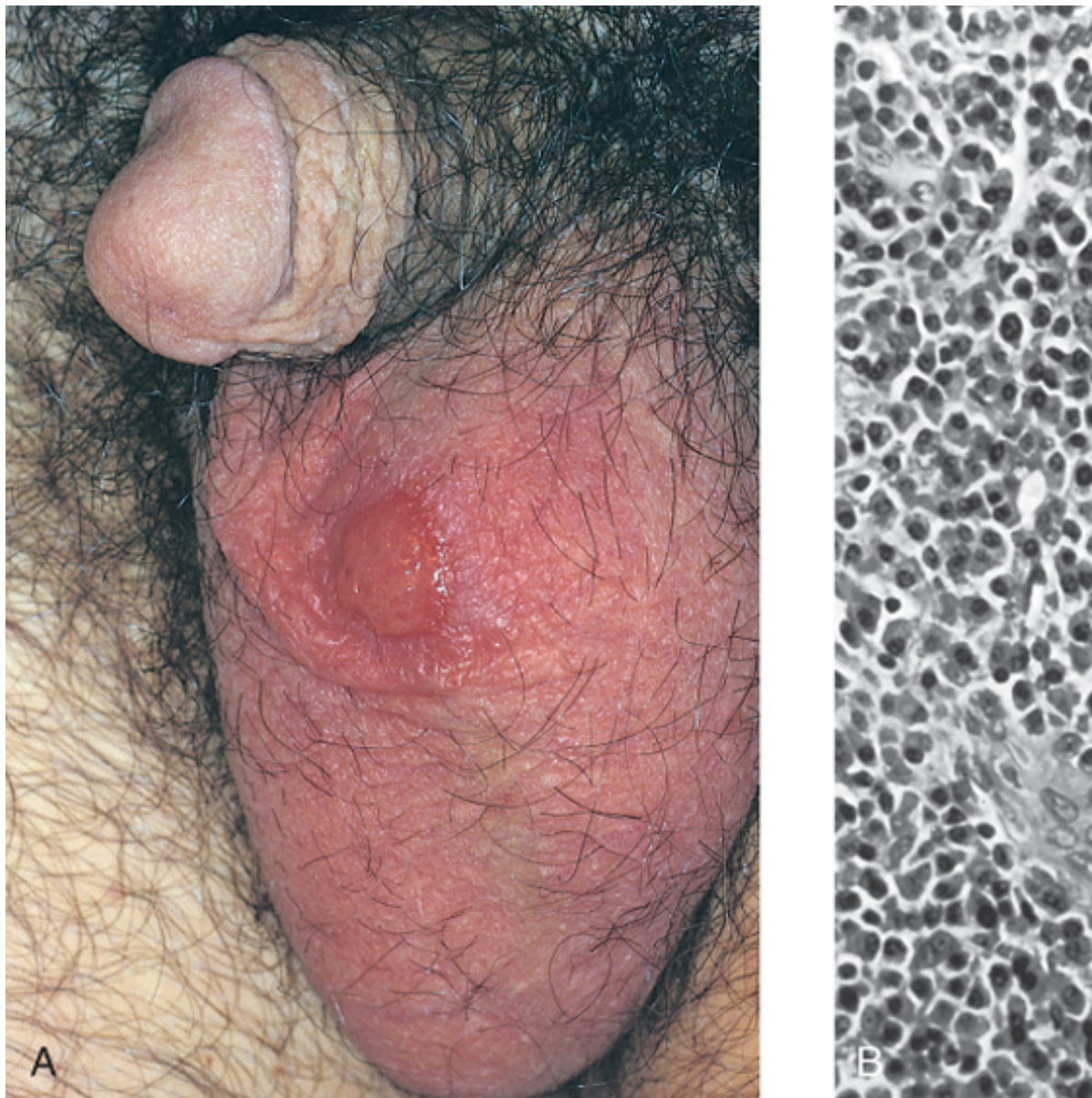
The macroscopic lesions of syphilis vary with the stage of disease and are discussed later. The microscopic lesion of syphilis is a **proliferative endarteritis** and an accompanying **rich in plasma cells**. The treponemes cause endothelial hypertrophy and proliferation of endothelial cells, leading to fibrosis and narrowing of the vessel lumen. Local ischemia caused by the vascular changes accounts for some of the local cell death and fibrosis seen in syphilis, although other factors, such as delayed hypersensitivity, also appear to contribute to parenchymal injury. Spirochetes are demonstrable in histologic sections of early lesions with the use of standard silver stains (e.g., Warthin-Starry). There is no evidence that the organisms cause direct toxic injury to the host. The parenchymal damage in tertiary syphilis results in the formation of a **gumma**, an irreversibly necrotic tissue surrounded by resilient connective tissue. Microscopically the gumma consists of coagulation necrosis surrounded by a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, activated macrophages (epithelioid cells), occasional giant cells, and a periplasmic zone of fibrous tissue.

### **Primary Syphilis**

This stage is characterized by the presence of a chancre at the site of initial inoculation. The chancre is a painless, indurated ulcer and has been referred to in the past as a "hard chancre" to distinguish it from the "soft chancre" caused by *Haemophilus ducreyi*; (discussed later). The primary chancre in males is usually on the penis. In females, it is usually in the vagina or on the uterine cervix. The chancre begins as a small, firm papule that evolves into a painless ulcer with well-defined, indurated margins and a "clean," moist base (Fig. 18-15). Spirochetes are often found in the exudate of the chancre.

scraped from the ulcer base using dark-field and immunofluorescence microscopy (Fig. 18-16). R enlarged and firm, but painless. Histologic examination of the ulcer reveals the usual lymphocytic and proliferative vascular changes as described before. Even without therapy, the primary chancre to form a subtle scar. *Serologic tests for syphilis are often negative during the early stages of pri* complemented by dark-field microscopy or direct fluorescent antibody testing if primary syphilis is

### Secondary Syphilis



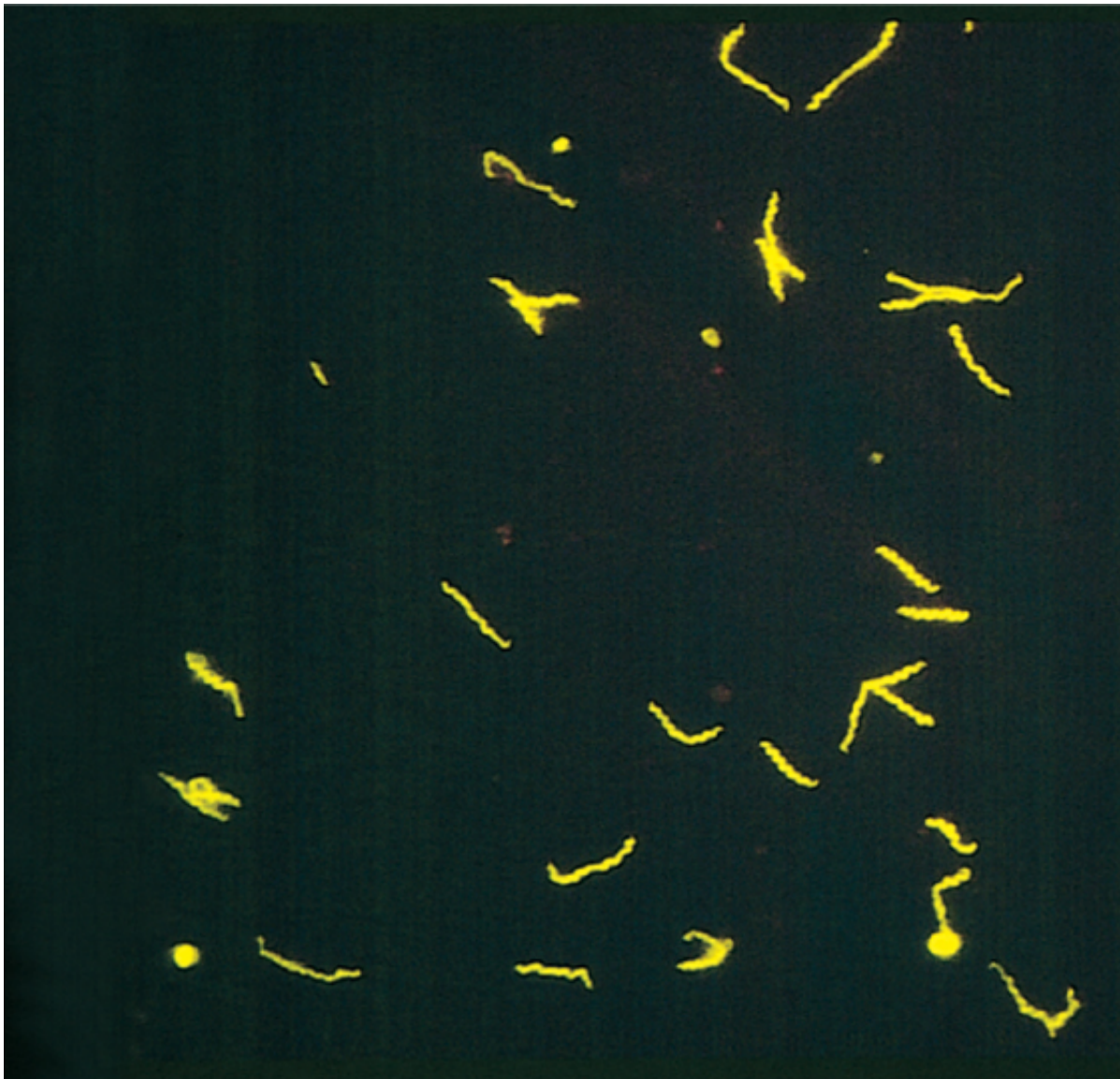
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Figure 18-15 **A**, Syphilitic chancre of the scrotum. Such lesions are typically painless despite the presence of ulcer of chancre with diffuse plasmacytic infiltrate and endothelial proliferation. (Courtesy of Dr. Richard Johnson, I Massachusetts.)

Within approximately 2 months of resolution of the chancre, the lesions of secondary syphilis occur syphilis are varied but typically include a combination of *generalized lymph node enlargement* and Skin lesions are usually symmetrically distributed and may be maculopapular, scaly, or pustular. */ soles of the feet is common* In moist skin areas, such as the anogenital region, inner thighs, and



sores of the foot is common. In moist skin areas, such as the anogenital region, minor thighs, and elsewhere, lesions termed *condylomata lata* may occur. Superficial mucosal lesions resembling condylomata lata can be particularly common in the oral cavity, pharynx, and external genitalia. Histologic examination of a skin lesion in the secondary phase of the disease reveals the characteristic *proliferative endarteritis*, accompanied by a mixed *infiltrate*. Spirochetes are present and easily demonstrable within the mucocutaneous lesions; the enlargement is most common in the neck and inguinal areas. Biopsy of enlarged nodes reveals no specific changes, but is accompanied by increased numbers of plasma cells or, less commonly, granulomas or neutrophils. Systemic manifestations of secondary syphilis include hepatitis, renal disease, eye disease (iritis), and gastrointestinal abnormalities. Lesions of secondary syphilis resolve over a period of several weeks, at which point the patient enters the early latent phase, which lasts approximately 1 year. Lesions may recur at any time during the early latent phase, during which the patient is *nontreponemal* and *antitreponemal* antibody tests are strongly positive in virtually all cases of secondary syphilis.

### **Tertiary Syphilis**



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 Figure 18-16 *Treponema pallidum* (dark-field microscopy) showing several spirochetes in scrapings from the base of a chancre. Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.

Tertiary syphilis develops in approximately one-third of untreated patients, usually after a latent period of 10 to 30 years. Tertiary syphilis is divided into three major categories: cardiovascular syphilis, neurosyphilis, and so-called gummas.

forms may occur singly or in combination in a given patient. *Nontreponemal antibody tests may be negative although antitreponemal antibody tests remain positive.*

Cardiovascular syphilis, in the form of *syphilitic aortitis*, accounts for more than 80% of cases of tertiary syphilis in men than in women. Briefly, the disease is fundamentally an endarteritis of the vasa vasorum of the aorta. Vasa vasorum results in scarring of the media of the proximal aortic wall, with consequent loss of elasticity. The disease is characterized by slowly progressive dilation of the aortic root and arch, with resultant aortic insufficiency. In some cases there is narrowing of the coronary artery ostia caused by subintimal scarring. The morphologic and clinical features of syphilitic aortitis are discussed in greater detail with disease progression.

*Neurosyphilis* accounts for only about 10% of cases of tertiary syphilis. Variants of neurosyphilis include *tabes dorsalis*, and a generalized brain parenchymal disease termed *general paresis*. They are distinguished by the increased frequency of neurosyphilis has been noted in patients with concomitant HIV infection.

A third, relatively uncommon, form of tertiary syphilis is the so-called benign tertiary syphilis, characterized by lesions in various sites. These lesions are probably related to the development of delayed hypersensitivity reactions. Lesions may occur in *bone, skin, and the mucous membranes of the upper airway and mouth*, although any organ may be affected. Characteristically causes local pain, tenderness, swelling, and, sometimes, pathologic fractures. In the mucous membranes may produce nodular lesions, or, in exceptional cases, destructive, ulcerative lesions. *Spirochetes are rarely demonstrable within the lesions.* Once common, gummas have become extremely rare since the use of effective antibiotics such as penicillin. They are reported now mostly in patients with AIDS.

### ***Congenital Syphilis***

*T. pallidum* may be transmitted across the placenta from an infected mother to the fetus at any time during pregnancy. Maternal transmission is greatest during the early (primary and secondary) stages of disease, when the concentration of bacteria in the blood is high. Because the manifestations of maternal disease may be subtle, routine serologic testing for syphilis is recommended. Stigmata of congenital syphilis typically do not develop until after the fourth month of pregnancy. In the absence of treatment, 40% of infected infants die in utero, typically after the fourth month.

Manifestations of *congenital syphilis* include stillbirth, infantile syphilis, and late (tardive) congenital syphilis. In stillborn, the most common manifestations are *hepatomegaly, bone abnormalities, pancreatic fibrosis, extramedullary hematopoiesis and portal tract inflammation.* Changes in the bones include inflammation at the osteochondral junction in long bones and, on occasion, bone resorption and fibrosis of the flat bones. The skin is pale as a result of the presence of inflammatory cells and fibrosis in the alveolar septa (pneumonia) demonstrable in tissue sections.

*Infantile syphilis* refers to congenital syphilis in liveborn infants that is clinically manifest at birth or within the first year of life. Affected infants present with chronic rhinitis (snuffles) and mucocutaneous lesions similar to those seen in secondary syphilis. Visceral and skeletal changes resembling those seen in stillborn infants may also be present.

*Late, or tardive, congenital syphilis* refers to cases of untreated congenital syphilis of more than 2 years' duration. It includes the Hutchinson triad: notched central incisors, interstitial keratitis with blindness, and deafness. Other changes include a saber shin deformity caused by chronic inflammation of the periosteum of the tibia ("mulberry" molars), chronic meningitis, chorioretinitis, and gummas of the nasal bone and cartilage deformity.

In cases of congenital syphilis, the placenta is enlarged, pale, and edematous. Microscopy reveals dilated fetal vessels, a mononuclear inflammatory reaction (villitis), and villous immaturity.

### ***Serologic Tests for Syphilis***

Although polymerase chain reaction (PCR)-based testing for syphilis has been developed, serologic testing remains the mainstay. Serologic tests for syphilis include nontreponemal antibody tests and antitreponemal antibody tests. Nontreponemal antibody tests include the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests. Nontreponemal antibody tests are positive after 1 to 2 weeks of infection and are usually positive by 4 to 6 weeks. Titers of these antibodies

positive after 1 to 2 weeks of infection and are usually positive by 4 to 6 weeks. None of these are used for treatment. The VDRL and RPR, widely used as screening tests for syphilis, are also used to monitor treatment. They are negative, however, in the late latent or tertiary phases of the disease. Nontreponemal antibodies rise after successful treatment. Two additional points about nontreponemal antibody tests deserve emphasis.

*Nontreponemal antibody tests are often negative during the early stages of disease, even in the primary stage. Hence, during this period, direct visualization of the spirochetes by dark-field or immunofluorescence can confirm the diagnosis. However, this requires rapid transit of specimens to the laboratory. Dark-field microscopy is not commonly performed, and treatment is based on clinical impressions. As many as 15% of patients have biologic false-positive results. These false-positive tests, which may be acute (transient) or chronic, increase in frequency with age. Conditions associated with false-positive VDRL results include certain diseases (e.g., systemic lupus erythematosus), drug addiction, pregnancy, hypergammaglobulinemia, and lepromatous leprosy.*

Treponemal antibody tests include the fluorescent treponemal antibody absorption test and the microhemagglutination-in-gel test for *Treponema pallidum* antibodies. These tests also become positive within 4 to 6 weeks after an infection. Unlike nontreponemal antibody tests, they remain positive indefinitely, even after successful treatment. They are not recommended for screening because they remain positive after treatment, and as many as 2% of the general population have positive results.

Serologic response may be delayed, exaggerated (false-positive results), or even absent in some cases of infection. However, in most cases, these tests remain extremely useful in the diagnosis and management of syphilis.

## SUMMARY

### Syphilis

Syphilis is an STD caused by *T. pallidum*, and has three stages. In primary syphilis, a painless ulcer called chancre develops on the external genitalia along with regional lymphadenopathy. Secondary syphilis presents with generalized lymphadenopathy and mucocutaneous lesions that may be maculopapular or take the form of flat raised lesions called condylomata lata. In tertiary syphilis, there is proximal aortitis with aortic insufficiency, and involvement of the brain, meninges, and bone. Maternal transmission of spirochetes, mostly during primary and secondary stages, causes congenital syphilis, which may result in stillbirth or widespread tissue injury in liver, spleen, lung, bones, and pancreas. Syphilitic lesions demonstrate proliferative endarteritis and a plasma cell-rich infiltrate. Gummas have a central area of necrosis surrounded by lymphoplasmacytic cells. Syphilis is diagnosed by direct demonstration of bacteria within the lesions in the primary or secondary stages or by serologic tests (all stages). Nontreponemal antibody tests are directed against treponemal cell wall and cross-react with host tissues. They become positive and are useful for screening, but they may be negative in the late latent or tertiary stages. A positive nontreponemal test may occur in SLE, in drug addicts, and during pregnancy. Specific antibody tests become positive later but remain positive indefinitely.

## Gonorrhea

Gonorrhea is a sexually transmitted infection of the lower genitourinary tract caused by *Neisseria gonorrhoeae*. Chlamydial infection of the genitourinary tract, discussed later, is the most common reproductive tract infection in the United States. With an estimated 650,000 cases each year in the United States it remains a major public health problem. The incidence of gonococcal infections is increased by the emergence of strains of *N. gonorrhoeae* that are resistant to penicillin.

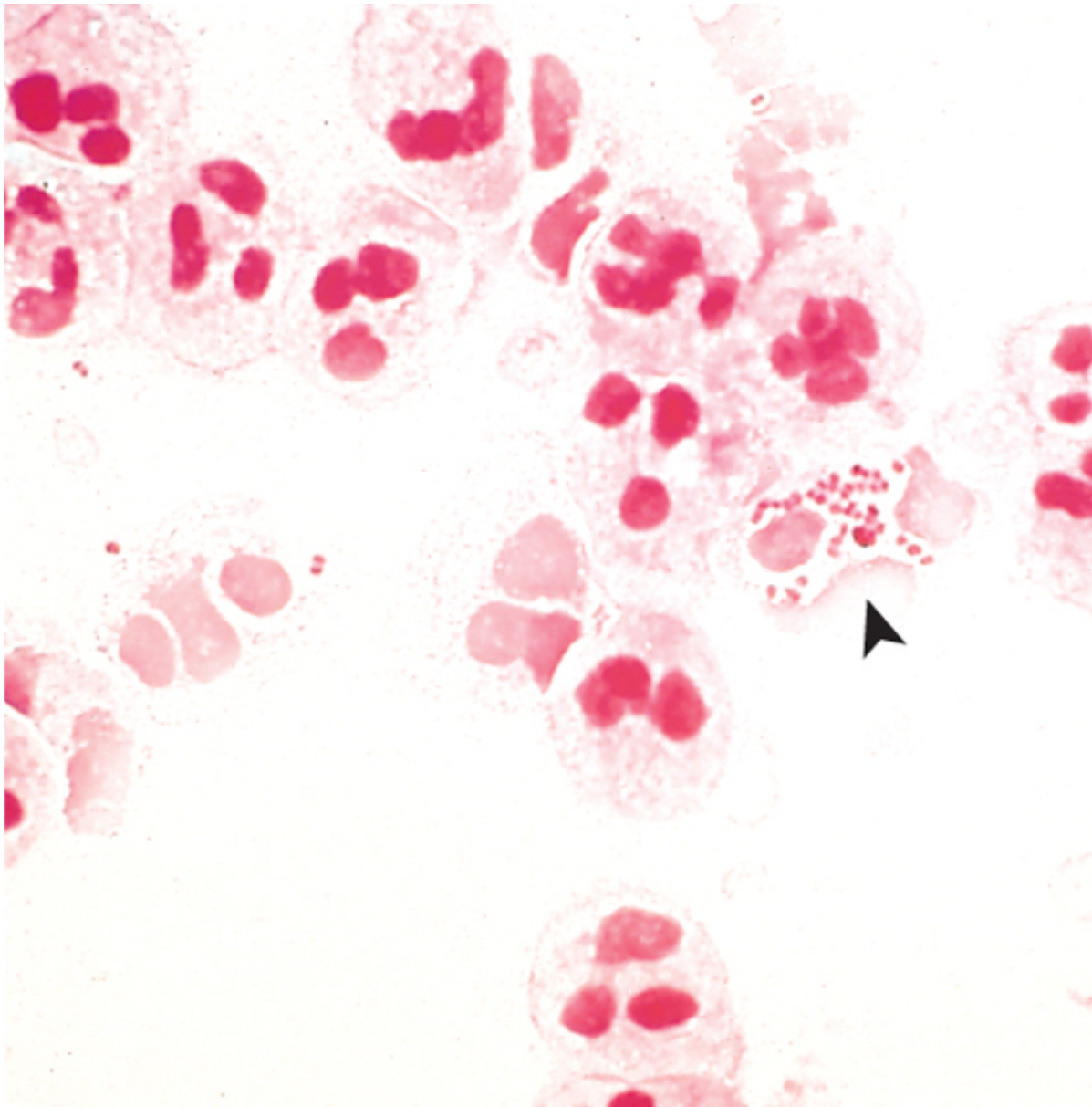
Humans are the only natural reservoir for *N. gonorrhoeae*. The organism is highly fastidious, and it is usually transmitted from one person to another, usually during sexual intercourse. There is no evidence that it can be transmitted by contact with toilet seats or other fomites. The bacteria initially attach to mucosal epithelium, particularly of the urethra, and attach to a variety of membrane-associated adhesion molecules and structures termed *pili* (Chapter 9). Such attachment is aided by being unceremoniously flushed by body fluids such as urine or endocervical mucus. The organism

cells and invades the deeper tissues of the host.

### **Morphology**

***N. gonorrhoeae*** provokes an intense, suppurative inflammatory reaction. In males often as a **purulent urethral discharge**, associated with an edematous, congested urethra. Gram-negative diplococci, many within the cytoplasm of neutrophils, are readily identified in the purulent exudate (Fig. 18-17). Ascending infection may result in the development of **epididymitis** (Fig. 18-18), and **orchitis**. Abscesses may complicate severe cases. In females, exudates tend to be less conspicuous in females, although acute inflammation of the Bartholin glands, is fairly common. Ascending infection involving the uterus, ovaries results in **acute salpingitis**, sometimes complicated by tubo-ovarian abscess. The inflammatory process is followed by the development of granulation tissue and scar tissue, strictures and other permanent deformities of the involved structures, giving rise to **disease**.

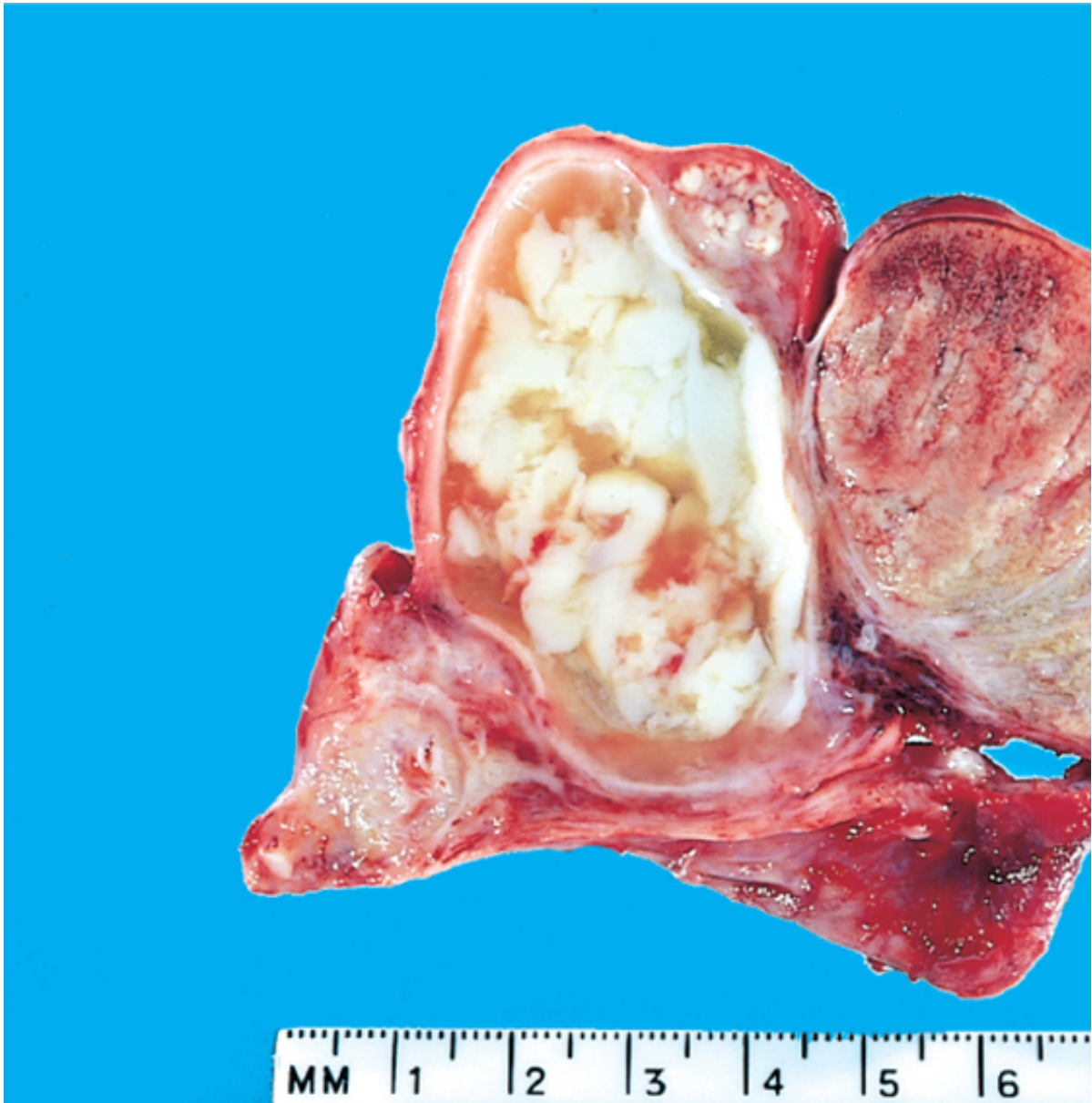
### *Clinical Features*







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Figure 18-17 *Neisseria gonorrhoeae*. Gram stain of urethral discharge, demonstrating characteristic gram-negative, Dr. Rita Gander, Department of Pathology, University of Texas Southwestern Medical S



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Figure 18-18 Acute epididymitis caused by gonococcal infection. The epididymis is replaced by an abs

In most infected males, gonorrhea is manifested by the presence of *dysuria*, *urinary frequency*, and *discharge* 2 to 7 days of the time of initial infection. Treatment with appropriate antimicrobial therapy results in resolution of symptoms. Untreated infections may ascend to involve the prostate, seminal vesicles, and may be complicated by chronic urethral stricture and, in more advanced cases, by permanent sterility. Chronic carriers of *N. gonorrhoeae*.

Among female patients, initial infection may be asymptomatic or associated with *dysuria*, *lower pelvic pain*, and *vaginal discharge*.

Among female patients, initial infection may be asymptomatic or associated with dysuria, lower pelvic pain, and vaginal discharge. Untreated cases may be complicated by ascending infection, leading to acute inflammation of the fallopian tubes. Chronic scarring of the fallopian tubes may occur, with resultant infertility and an increased risk of ectopic pregnancy. Infection of the upper genital tract may spread to the peritoneal cavity, where the exudate may extend up to the liver, resulting in gonococcal perihepatitis.

Other sites of primary infection, more commonly encountered in male homosexuals than in heterosexuals, are the rectum and anorectal area, with resultant acute proctitis and proctitis, respectively.

*Disseminated infection* is much less common than local infection, occurring in 0.5% to 3% of cases in females than males. Manifestations include, most commonly, tenosynovitis, arthritis, and pustular lesions. Meningitis and endocarditis are rare manifestations. Strains that cause disseminated infection are usually resistant to penicillin.

*Gonococcal infection may be transmitted to infants* during passage through the birth canal. The acute infection of the eyes (ophthalmia neonatorum), an important cause of blindness in the past. The reduction in the use of mercury to the eyes of newborns has resulted in a marked reduction in the incidence of this disorder.

Both culture and nucleic acid amplification techniques can be used for diagnosis of gonococcal infection. Culture is the gold standard, but it can be done on nongenital sources such as eye and rectum, and antibiotic sensitivity can be determined. Nucleic acid amplification methods can usually be done on urine and urethral samples. They are somewhat more sensitive than culture, but are being used increasingly.

## SUMMARY

### Gonorrhea

Gonorrhea is a common STD affecting the genitourinary tract that can become life-threatening in individuals with deficiency of complement. In males there is a severe, symptomatic infection that can spread to the prostate, epididymis, and testis. In females the initial lesions are less prominent than in males, but ascending infection to fallopian tubes can result in scarring and deformity with resultant sterility. Pregnant females can transmit the infection during passage through the birth canal. Diagnosis can be made by culture or by nucleic acid amplification techniques.

## Nongonococcal Urethritis and Cervicitis

Nongonococcal urethritis (NGU) and cervicitis are the most common forms of STDs today. A variety of organisms can cause the pathogenesis of NGU and cervicitis, including *C. trachomatis*, *Trichomonas vaginalis*, *U. urealyticum*, and *Mycoplasma genitalium*. Most cases are apparently caused by *C. trachomatis*, and this organism is believed to be the most common cause of NGU in the United States. *U. urealyticum* is the next most common cause of NGU.

*C. trachomatis* is a small gram-negative bacterium that is an obligate intracellular parasite. It exists in a so-called elementary body, is capable of at least limited survival in the extracellular environment. It enters host cells, primarily via a process of receptor-mediated endocytosis. Once inside the cell, the elementary body becomes the active form, termed the *reticulate body*. Using energy sources from the host cell, the reticulate body becomes elementary bodies capable of infecting additional cells. They preferentially infect columnar epithelium.

*C. trachomatis* infections may be associated with a spectrum of clinical features that are virtually identical to those of gonorrhea. Thus, patients may develop epididymitis, proctitis, pelvic inflammatory disease, proctitis, inflammation, and, among persons engaging in anal intercourse, proctitis. *C. trachomatis* also causes conjunctivitis, discussed in the next section.

The morphologic and clinical features of chlamydial infection, with the exception of lymphogranuloma venereum, are those of gonorrhea. The primary infection is characterized by a *mucopurulent discharge containing* gonococci. Organisms are not visible in gram-stained sections. In contrast to the gonococcus, *C. trachomatis* does not grow on conventional culture media. The diagnosis is best made by nucleic acid amplification tests on vaginal or urethral secretions.

from genital swabs, it is not possible from urine. Molecular tests are also more sensitive than culture. Infection can include a reactive arthritis, predominantly in patients who are HLA-B27 positive. This condition typically presents as a combination of urethritis, conjunctivitis, arthritis, and generalized mucocutaneous lesions.

## SUMMARY

### Nongonococcal Urethritis and Cervicitis

NGU and cervicitis are the most common STDs. The majority are caused by *T. vaginalis*, *U. urealyticum*, and *M. genitalium*. *C. trachomatis* is a gram-negative bacterium that causes a disease that is clinically indistinguishable from gonorrhea in men and women. Diagnosis requires detection of the bacteria by molecular methods. Culture from genital swabs is possible but requires special methods. In patients who are HLA-B27 positive, infection can cause reactive arthritis along with conjunctivitis, and generalized mucocutaneous lesions, together called Reiter syndrome.

### Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a chronic, ulcerative disease caused by certain strains of *C. trachomatis* those causing the more common NGU or cervicitis discussed before. It is a sporadic disease in the United States but is endemic in parts of Asia, Africa, the Caribbean region, and South America. As in the case of gonorrhea, sporadic cases of LGV are associated most often with sexual promiscuity.

#### Morphology

The patient with LGV may present with nonspecific urethritis, papular or ulcerative genitalia, regional adenopathy, or an anorectal syndrome. The lesions contain a **neutrophilic inflammatory response**, with a variable number of chlamydial inclusions within epithelial cells or inflammatory cells. Regional lymphadenopathy is common, usually appearing within a few days of the time of infection. Lymph node involvement is characterized by a granulomatous reaction associated with irregularly shaped foci of necrosis and neutrophilic infiltration (**stellate** in appearance). At the time, the inflammatory reaction gives rise to extensive fibrosis that can cause local **lymphedema** and strictures. Rectal strictures are particularly common in women. In the acute phase, diagnosis of LGV may be made by demonstration of the organism in biopsy sections. In more chronic cases, the diagnosis rests on the demonstration of antibodies to the organism in the patient's serum. Nucleic acid amplification tests have also been developed for the diagnosis of LGV.

### Chancroid (Soft Chancre)

Chancroid, sometimes called the "third" venereal disease (after syphilis and gonorrhea), is an acute infection caused by *Haemophilus ducreyi*, a small, gram-negative coccobacillus. The disease is most common in tropical and subtropical regions, prevalent in lower socioeconomic groups, particularly among men who have regular contact with multiple sexual partners. It is a *common cause of genital ulcers in Africa and southeast Asia*, where it serves as an important cause of genital ulcer disease. Chancroid is probably underdiagnosed in the United States, because most STD clinics do not routinely culture for *ducreyi*, and PCR-based tests are not widely available.

#### Morphology

Four to seven days after inoculation, the person with chancroid develops a tender, painful ulcer, involving the external genitalia. In males the primary lesion is usually on the penis; in females, ulcers occur in the vagina or periurethral area. Over the course of several days the surface of the ulcer erodes to produce an **irregular ulcer**, which is more likely to be painful in males than in females. Unlike the primary chancre of syphilis, the ulcer of chancroid is not indurated, and multiple ulcers may be present. The base of the ulcer is covered by shaggy, yellow-gray exudate. The regional lymph nodes, particularly in the inguinal region, become enlarged and tender in about 50% of cases, usually within a few days of the primary inoculation. In untreated cases, the inflamed and enlarged nodes (buboes) may break through the overlying skin to produce chronic, draining ulcers.

Microscopically, the ulcer of chancroid contains a superficial zone of neutrophilic discharge.

underlying zone of granulation tissue containing areas of necrosis and thrombosed lymphoplasmacytic inflammatory infiltrate is present beneath the layer of granulation tissue. The organisms are sometimes demonstrable in Gram or silver stains, but they are often not. Bacterial growth is frequently present at the ulcer base. In the majority of cases, *H. ducreyi* is the organism when appropriate media are used.

## Granuloma Inguinale

Granuloma inguinale is a chronic inflammatory disease caused by *Calymmatobacterium granulomatis* related to the *Klebsiella* genus. This disease is uncommon in the United States and areas in certain tropical and subtropical regions. When it occurs in urban settings, transmission is often associated with sexual promiscuity. Untreated cases are characterized by extensive scarring, often associated with lymphedema (elephantiasis) of the external genitalia. Culture of the organism is difficult, and PCR

### Morphology

Granuloma inguinale begins as a raised, papular lesion involving the moist, stratified squamous epithelium of the genitalia. The lesion eventually undergoes ulceration, accompanied by the development of granulation tissue, which is manifested grossly as a protuberant, soft, painless mass. The borders become raised and indurated. Disfiguring scars may develop in untreated cases. Sometimes associated with urethral, vulvar, or anal strictures. Regional lymph nodes show only nonspecific reactive changes, in contrast to chancroid.

Microscopic examination of active lesions reveals marked epithelial hyperplasia at the base of the ulcer, sometimes mimicking carcinoma (**pseudoepitheliomatous hyperplasia**). A mixture of mononuclear inflammatory cells is present at the base of the ulcer and beneath the ulcer crust. The organisms are demonstrable in Giemsa-stained smears of the exudate as small, bipolar, rod-shaped bacteria. Silver stains (e.g., the Warthin-Starry stain) can demonstrate the organism.

## SUMMARY

### Lymphogranuloma Venereum, Chancroid, and Granuloma Inguinale

LGV is caused by *C. trachomatis* serotypes that are distinct from those that are associated with urethritis, ulcerative genital lesions, lymphadenopathy, and proctitis. The lesions show both acute and chronic inflammation; they progress to fibrosis and rectal strictures. *H. ducreyi* infection causes an acute painful ulcerative lesion called *chancroid*. Inguinal node involvement occurs in many cases and leads to the formation of buboes. Ulcers show a superficial area of acute inflammation and necrosis overlying a zone of granulation tissue and mononuclear infiltrate. Diagnosis is possible by culture of the organism. *Granuloma inguinale* is a chronic fibrosing STD caused by *C. granulomatis*. It begins as a papular lesion on the genitalia that expands, ulcerates, and may cause urethral, vulvar, or anal strictures. Microscopically there is granulation tissue and intense epithelial hyperplasia, sometimes mimicking squamous cell carcinoma. Organisms are visible as small intracellular coccobacilli within macrophages (Donovan bodies).

## Trichomoniasis

*T. vaginalis* is a sexually transmitted protozoan that is a frequent cause of vaginitis. The trophozoite causes superficial lesions of the mucosa. In females, *T. vaginalis* infection is often associated with loss of normal vaginal flora. It can be asymptomatic, but frequently it causes itching and a profuse, frothy, yellow vaginal discharge. Frequency and dysuria. *T. vaginalis* infection is usually asymptomatic in males but in some cases it causes urethritis. The organism is usually demonstrable in smears of vaginal scrapings.

## Genital Herpes Simplex



Genital herpes infection, or herpes genitalis, is a common STD that affects an estimated 50 million. Both herpes simplex virus 1 (HSV-1) and HSV-2 can cause genital or oral infections, most cases of which are caused by HSV-2. Current studies reveal that an increasing number of genital infections are being caused by HSV-1 through oral sex. Genital HSV infection may occur in any sexually active population. As with other STDs, the number of sexual contacts influences the risk of infection. HSV is transmitted when the virus comes into contact with a mucocutaneous susceptible host. Such transmission requires direct contact with an infected person, because the virus is sensitive to heat and drying, particularly if dried.

### **Morphology**

The initial lesions of genital HSV infection are **painful, erythematous vesicles** on the lower genitalia and adjacent extra-genital sites. The anorectal area is a particularly common site of infection among homosexual males. Histologic changes include the presence of **intranuclear inclusions** accompanied by necrotic cellular debris, neutrophils, and cells harboring characteristic **Cowdry type A inclusions**. The classic **Cowdry type A inclusion** appears as a light purple, homogenous structure surrounded by a clear halo. Infected cells commonly fuse to form multinucleated giant cells. Inclusions readily stain with antibodies to HSV, permitting a rapid, specific diagnosis on immunofluorescent histologic sections or smears.

As mentioned earlier, both HSV-1 and HSV-2 can cause genital or oral infection, and both can produce mucocutaneous lesions that are clinically indistinguishable. The manifestations of HSV infection vary depending on whether the infection is primary or recurrent. Primary infection is often mildly symptomatic with HSV-2. An initial episode, locally painful vesicular lesions are often accompanied by dysuria, urethral discharge, local tenderness, and systemic manifestations, such as fever, muscle aches, and headache. HSV is shed from lesions and continues to be shed until the mucosal lesions have completely healed. Signs and symptoms may recur. Recurrences are much more common with HSV-1 than HSV-2 and are typically triggered by stress or a primary episode. As with primary infection, HSV is shed while active lesions are present.

Among immunocompetent adults, herpes genitalis is generally not life-threatening. However, HSV infection in immunosuppressed patients, in whom fatal, disseminated disease may develop. *Neonatal herpes* is a severe disease delivered vaginally of mothers suffering from either primary or recurrent genital HSV infection. The passage through the birth canal. Its incidence has risen in parallel with the rise in genital HSV infection. Neonatal herpes, which typically develop during the second week of life, include rash, encephalitis, pneumonia, and disseminated disease. Approximately 60% of affected infants die of the disease, with significant morbidity occurring in survivors. The diagnosis of genital herpes relies on viral culture. Molecular diagnostic tests are also available but are not yet widely used, particularly in central nervous system infections.

### **Human Papillomavirus Infection**

HPV is the cause of a number of squamous proliferations in the genital tract, including condyloma lesions, and some carcinomas ([Chapter 19](#)). *Condylomata acuminata*, also known as venereal warts, are common lesions. They occur on the penis as well as on the female genitalia. They should not be confused with the lesions of syphilis. Genital HPV infection may be transmitted to neonates during vaginal delivery. These infants develop benign and potentially life-threatening papillomas of the upper respiratory tract.

### **Morphology**

In males, condylomata acuminata usually occur on the coronal sulcus or inner surface of the prepuce. They range from small, sessile lesions to large, papillary proliferations measuring several centimeters in diameter. In females, they commonly occur on the vulva (see [Fig. 19-2](#); [Chapter 19](#)). The gross appearance is that of an exuberant proliferation of stratified squamous epithelium composed of numerous papillae. The more superficial epithelial cells contain irregular, hyperchromatic nuclei. A characteristic clear perinuclear halo, a change referred to as **koilocytosis** (see [Fig. 19-2](#)), is often present.

## **SUMMARY**

### **Herpes Simplex Virus and Human Papillomavirus**

HSV-2, and less commonly HSV-1, can cause genital infections. Initial (pruritic, painful, erythematous, intraepithelial vesicles on the mucosa and skin of external genitalia, regional lymph node enlargement. Recurrent lesions are more common with primary lesions. They are milder. Histologically, the vesicles contain necrotic cells and fused multinucleated giant cells containing purple, intranuclear inclusions (Cowdry's type A) that stain with a hematoxylin and eosin stain. Herpes can be life threatening and occurs in children born to mothers with genital herpes. Infants have generalized herpes including encephalitis and consequent high mortality. Many proliferative lesions of the genital mucosa including condyloma acuminatum and frank cancers. Condylomas are papillary proliferations in which the superficial cells show koilocytic changes.

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## 19 The Female Genital System and Breast

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VINAY KUMAR MD

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### VULVA

Clinically significant diseases of the vulva do not loom large in gynecologic practice. Only the uncommon carcinomas are life threatening. Far more frequent are the inflammatory disorders (vulvitis), which are more uncomfortable than serious. Only a few other conditions bear mentioning here: non-neoplastic epithelial disorders (discussed later); the painful Bartholin cysts caused by obstruction of the excretory ducts of the glands; and imperforate hymen in children, impeding secretions and menstrual flow later in life.



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## VULVA

Clinically significant diseases of the vulva do not loom large in gynecologic practice. Only the uncommon carcinomas are life threatening. Far more frequent are the inflammatory disorders (vulvitis), which are more uncomfortable than serious. Only a few other conditions bear mentioning here: non-neoplastic epithelial disorders (discussed later); the painful Bartholin cysts caused by obstruction of the excretory ducts of the glands; and imperforate hymen in children, impeding secretions and menstrual flow later in life.







## VULVITIS

The moist hair-bearing skin and delicate membrane of the vulva are vulnerable to many nonspecific microbe-induced inflammations and dermatologic disorders. Intense itching (pruritus) and subsequent scratching often exacerbate the primary condition. There are also many specific forms of vulvar infection related to sexually transmitted diseases. Most are discussed in [Chapter 18](#). The five most important of these infectious agents in North America are human papillomavirus (HPV), producing condylomata acuminata and vulvar intraepithelial neoplasia (both discussed in some detail later); herpes genitalis (herpes simplex virus [HSV 1 or 2]), causing a vesicular eruption; gonococcal suppurative infection of the vulvovaginal glands; syphilis, with its primary chancre at the site of inoculation; and candidal vulvitis.

### Contact Dermatitis

One of the most common causes of vulvar pruritus is a reactive inflammation to an exogenous stimulus, whether an irritant (contact irritant dermatitis) or an allergen (contact allergic dermatitis). Irritant dermatitis presents as well-defined erythematous weeping and crusting papules and plaques and may be a reaction to urine, soaps, detergents, antiseptics, deodorants, or alcohol. Allergic dermatitis has a similar gross appearance and may result from allergy to perfumes and other additives in creams, lotions, and soaps, chemical treatments on clothing, and other antigens. Both forms of contact dermatitis may present as an acute spongiotic dermatitis or as a subacute dermatitis with epithelial hyperplasia or subacute dermatitis (see [Chapter 22](#)).

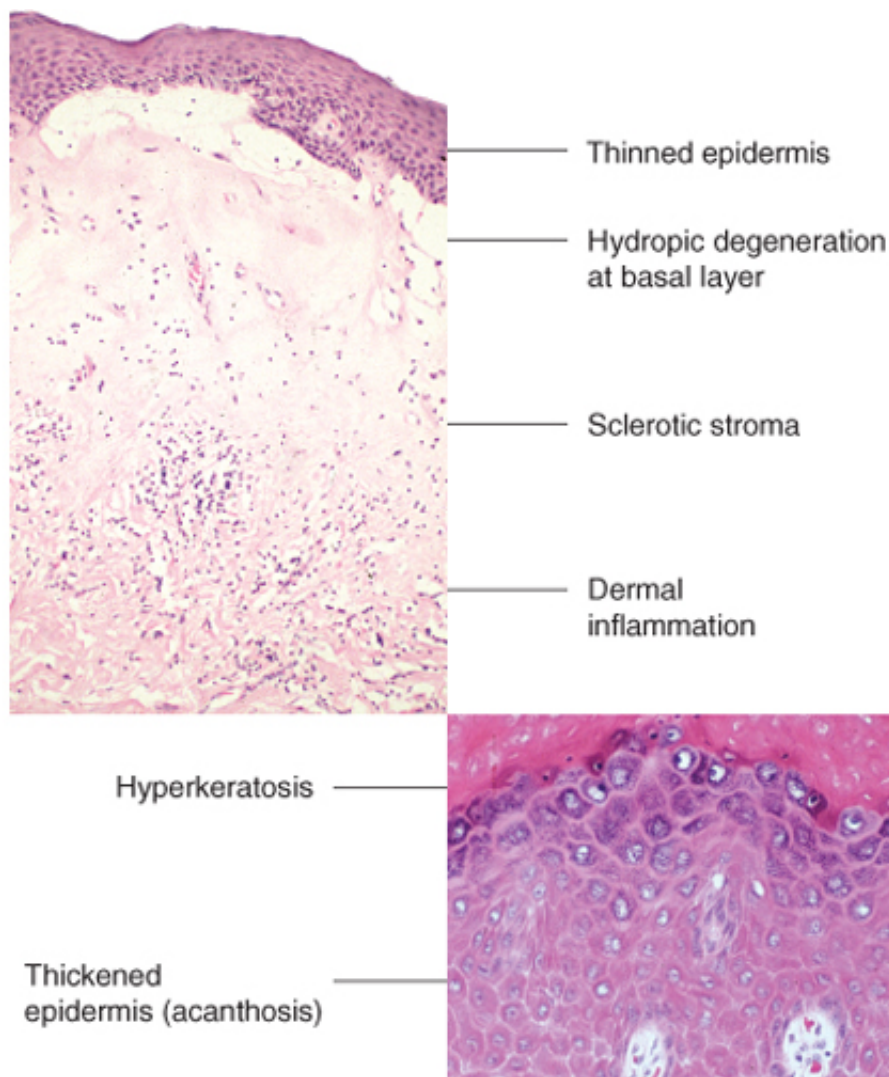


## NON-NEOPLASTIC EPITHELIAL DISORDERS

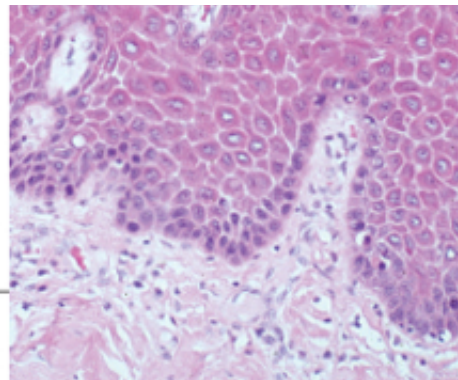
The epithelium of the vulvar mucosa may undergo atrophic thinning or hyperplastic thickening. For want of a better term, these alterations were previously referred to as "dystrophies" but are now simply referred to as non-neoplastic epithelial disorders to differentiate them from the premalignant lesions discussed later. There are two forms of non-neoplastic epithelial disorders: lichen sclerosus and lichen simplex chronicus. Both may coexist in different areas in the same person, and both may appear macroscopically as depigmented white lesions, referred to as *leukoplakia*. Similar white patches or plaques are also seen with (1) vitiligo (loss of pigment) of the skin, (2) a variety of benign dermatoses such as psoriasis and lichen planus ([Chapter 22](#)), (3) carcinoma in situ, (4) Paget disease (described later), and (5) invasive carcinoma. Thus, leukoplakia is merely a descriptive term that gives no indication of its underlying nature. Only biopsy and microscopic examinations can differentiate among these similar-looking lesions.

### Lichen Sclerosus

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Dermal inflammation



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Figure 19-1 Inflammatory vulvar disorders. Lichen sclerosus (*upper panel*). Lichen simplex chronicus (*lower panel*). The main features of the lesions are indicated in the figures.

This lesion is characterized by thinning of the epidermis and disappearance of rete pegs, hydropic degeneration of the basal cells, superficial hyperkeratosis, and dermal fibrosis with a scant perivascular, mononuclear inflammatory cell infiltrate (Fig. 19-1). The lesions appear clinically as smooth, white plaques or papules that in time may extend and coalesce. The surface is smoothed out and sometimes resembles parchment. When the entire vulva is affected, the labia become somewhat atrophic and stiffened, and the vaginal orifice is constricted. It occurs in all age groups but is most common in postmenopausal women. It may also be encountered elsewhere on the skin. The pathogenesis is uncertain, but the presence of activated T cells in the subepithelial inflammatory infiltrate and the increased frequency of autoimmune disorders in these women suggests an autoimmune reaction may be involved. Although the lesion in lichen sclerosus is not pre-malignant by itself, women with symptomatic lichen sclerosus have approximately a 15% chance of developing squamous cell carcinoma in their lifetime.

### Lichen Simplex Chronicus

Previously called "hyperplastic dystrophy," this disorder is the end stage of many inflammatory dermatoses and is marked by epithelial thickening, expansion of the stratum granulosum, and significant surface hyperkeratosis. It appears clinically as an area of leukoplakia. The epithelium may show increased mitotic activity in both the stratum basalis and spinosum. Leukocytic infiltration of the dermis is sometimes pronounced. The hyperplastic epithelial changes show no atypia (see Fig. 19-1). There is generally no increased predisposition to cancer, but suspiciously, lichen simplex chronicus is often present at the margins of established cancer of the vulva.

### SUMMARY

#### Non-neoplastic Epithelial Disorders

Lichen sclerosus is characterized by atrophic epithelium, usually with dermal fibrosis. Lichen sclerosus carries an increased risk of developing squamous cell carcinoma. Lichen simplex chronicus is characterized by thickened epithelium, usually with an inflammatory infiltrate.





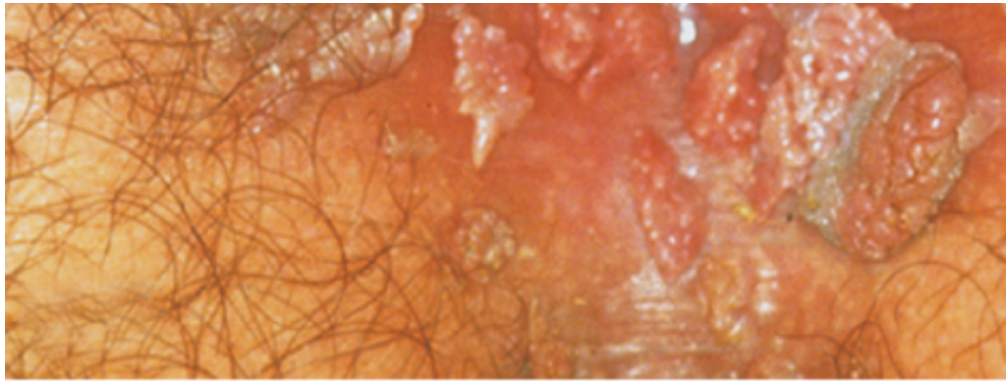
## TUMORS

### Condylomas and Low-Grade Vulvar Intraepithelial Neoplasia (VIN)

Condylomas are essentially anogenital warts, but in the moist environment of the vulva they tend to take on a variety of biologic forms, but rarer types also exist. *Condylomata lata*, not commonly seen today, are flat, moist lesions seen in secondary syphilis ([Chapter 18](#)). The more common *condylomata acuminata* may be papillary and rugose. They occur anywhere on the anogenital surface, sometimes singly but more often in clusters. They range from a few millimeters to many centimeters in diameter and are red-pink to pink-brown ([Fig. 19-2](#)). The histologic lesions were described earlier ([Chapter 18](#)), but particularly significant is the characteristic cellular atypia, including cytoplasmic vacuolization with nuclear angular pleomorphism and koilocytosis ([Fig. 19-3](#)). Such lesions are caused by HPV infection. Indeed, there is a strong association with HPV 6 and HPV 11. The HPV can be transmitted by sexual contact. Vulvar condylomas are not precancerous but may be associated with low-grade intraepithelial neoplasia in the vulva (VIN grade I) and cervix. Indeed, according to some authorities, VIN I and VIN II have a low malignant potential, should be segregated from VIN II and VIN III, discussed later. The types of HPV most often found in condylomas are HPV 6 and HPV 11.





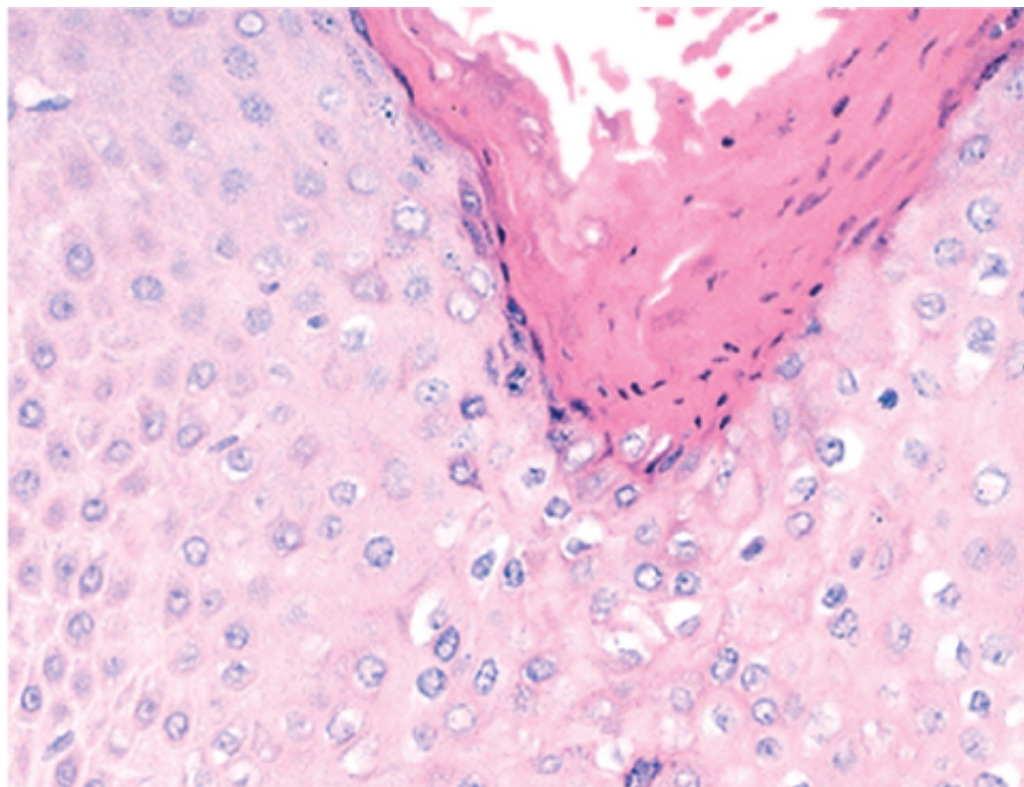


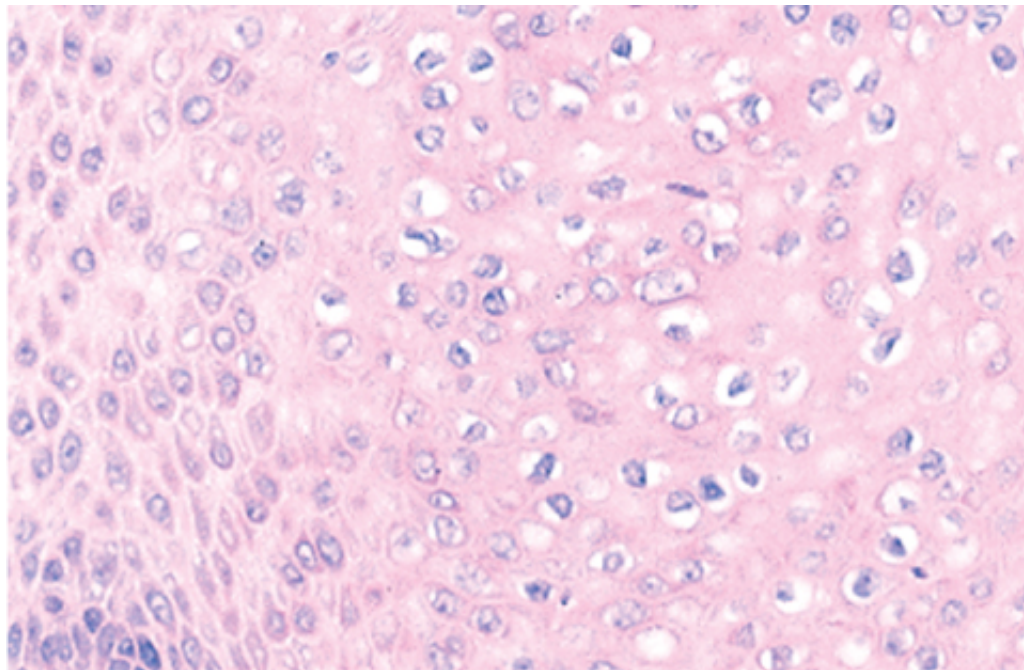
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Figure 19-2 Numerous condylomas of the vulva. (Courtesy of Dr. Alex Ferenczy, McGill Universit

### High-Grade Vulvar Intraepithelial Neoplasia and Carcinoma of the Vulva

Carcinoma of the vulva represents about 3% of all genital tract cancers in women, occurring most commonly in women older than 60 years of age. However, there has been an increase in the frequency of high grade VIN in the past few decades, particularly in younger women (median age, 60 years of age). In all age groups, approximately 90% of carcinomas are squamous cell carcinomas, with the remainder being adenocarcinomas, melanomas, or basal cell carcinomas.

Many findings suggest that there are two biologic forms of vulvar carcinoma. The most common is squamous cell carcinoma, which is particularly associated with cigarette smoking. HPV, especially type 16 and less frequently other types, is present in many cases; there is coexisting vaginal or cervical carcinoma, carcinoma in situ, or condylomata acuminata in many cases, probably HPV. Often in these women, in situ cancerous changes (i.e. VIN) confined to the epithelium precede the development of an invasive cancer. The VIN may be graded VIN I, VIN II, or VIN III (carcinoma in situ). It may be found in multiple, separate foci, or associated with an invasive lesion. Whether VIN is always destined to become an invasive cancer remains uncertain. In at least some individuals, the VIN has been present for many years, perhaps decades. Whether genetic and environmental influences (e.g., cigarette smoking or superinfection with new strains of HPV) determine the course of the disease remains uncertain.





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Figure 19-3 Histopathology of condyloma acuminatum showing acanthosis, hyperkeratosis, and cytoplasmic vacuolization.

The other subgroup of vulvar carcinoma occurs in older women. It is not associated with HPV but with neoplastic epithelial changes, principally lichen sclerosus and, rarely, lichen simplex chronicus. For the typical cytologic changes of VIN, but it may display dyskeratotic cells, angular budding, and bizarre changes of VIN precede the appearance of the overt neoplasm. Tumors tend to be well differentiated.

### Morphology

VIN and early vulvar carcinomas appear as areas of **leukoplakia** caused by epithelial changes in any region of the vulva or adjacent skin. In about one-fourth of cases the lesions are exophytic. In the course of time, these areas are transformed into overt **exophytic** or ulcerative tumors. HPV-positive tumors are more often multifocal and appear warty or condylomatous.

Histologically, HPV-positive neoplasms tend to be poorly differentiated **squamous** cell carcinomas. The HPV-negative lesions, which are usually unifocal, tend to show well-differentiated squamous cells. Although all patterns tend to remain confined to their site of origin for a few years, local invasion with involvement of regional nodes and lymphohematogenous spread occurs. Spread is correlated with the size of the tumor and the depth of invasion.

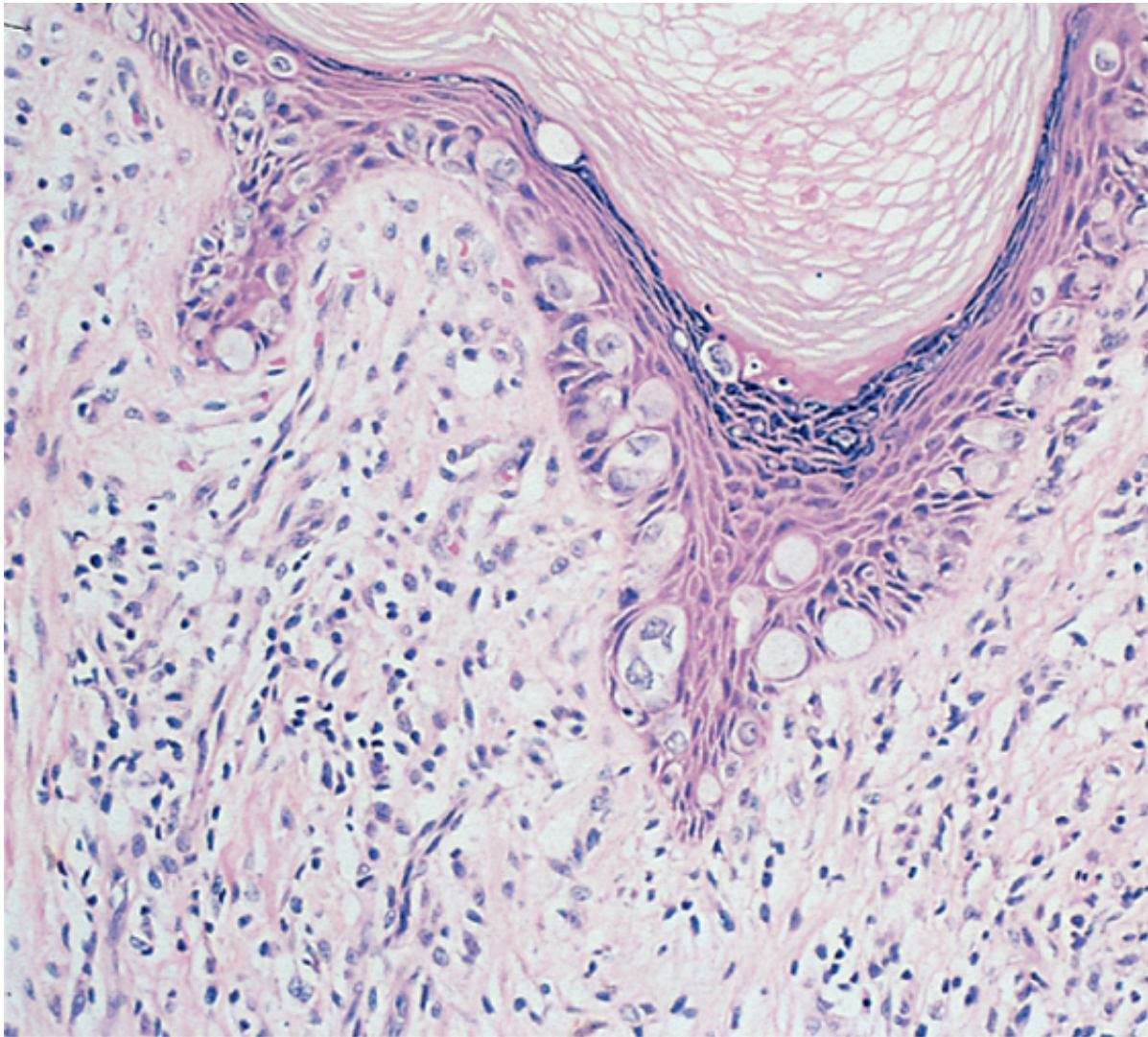
Women with a tumor less than 2 cm in diameter have about a 75% 5-year survival after radical excision. Larger lesions survive 10 years.

### Extramammary Paget Disease

Paget disease of the vulva, like that of the breast, is essentially a form of intraepithelial carcinoma. It is virtually always associated with an underlying carcinoma, the majority of cases of vulvar Paget disease arising from an underlying adenocarcinoma. Occasionally there is an accompanying subepithelial or submucosal tumor arising in the glands. In cases without an underlying primary, the tumor likely arises from aberrant differentiation of the epidermis.







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Figure 19-4 Paget disease of the vulva, with scattered large, clear tumor cells within the

Vulvar Paget disease presents as a red, scaly, crusted plaque and may appear as an inflammatory infiltrate. Epithelioid cells infiltrate the epidermis, singly and in groups, with abundant granular cytoplasm and nuclei (Figure 19-4) containing mucin that stains positive for periodic acid-Schiff. When the Paget cells are confined to the epidermis, the disease is called Paget disease of the vulva. It can persist for years or even decades without evidence of invasion. However, in some instances, particularly in the case of an appendageal tumor, the Paget cells extend into the skin appendages, invade locally, and ultimately metastasize, usually within the first 2 to 5 years.

### **SUMMARY**

#### **Squamous Carcinoma of the Vulva**

As many as 90% of vulvar squamous cell carcinomas are HPV related, usually well-differentiated lesions, sometimes multifocal. They often evolve from vulvar intraepithelial neoplasia. Non-HPV-related vulvar squamous cell carcinoma occurs in older women, is usually well-differentiated and unifocal, and is associated with lichen sclerosus or other preexisting conditions.

#### **Paget Disease of the Vulva**

Red, scaly plaque, microscopically characterized by the spread of malignant cells within the epidermis.

epithelium, occasionally with invasion of underlying dermis in a minority of cases. Carcinoma of a vulvar or perineal gland



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## VAGINA

The vagina in adults is seldom the site of primary disease. More often it is secondarily involved in the spread of cancer or infections arising in close proximity (e.g., cervix, vulva, bladder, rectum). The only primary disorders discussed here are a few congenital anomalies, vaginitis, and primary tumors.

Congenital anomalies of the vagina are fortunately uncommon and include entities such as total absence of the vagina, a septate or double vagina (usually associated with a septate cervix and, sometimes, uterus), and congenital small lateral Gartner duct cysts arising from persistent embryonic remnants.





## VAGINITIS

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Vaginitis is a relatively common clinical problem that is usually transient and not serious. It produces a vaginal discharge (leukorrhea). A large variety of organisms have been implicated, including bacteria, fungi, and parasites. Many represent normal commensals that become pathogenic in conditions such as diabetes, systemic antibiotic therapy that disrupts the normal microbial flora, after abortion or pregnancy, or in elderly persons with compromised immune function, and in patients with the acquired immunodeficiency syndrome. In adults, primary gonorrheal infection of the vagina is uncommon. However, it may occur in a newborn born to an infected mother. The only other organisms worthy of specific mention, because they are frequent offenders, are *Candida albicans* and *Trichomonas vaginalis*. Candidal (monilial) vaginitis produces a curdy white discharge. This organism is present in about 5% of normal adults, and so the appearance of symptomatic infection almost always involves predisposing influences or sexual transmission of a new, more aggressive strain. Biopsy specimens, which are rarely obtained, reveal only superficial, nonspecific submucosal inflammation. *T. vaginalis*, also a frequent offender, produces a watery, copious gray-green discharge in which parasites can also be identified microscopically. However, *Trichomonas* can also be identified in about 10% of asymptomatic women, and so active infection usually represents a sexually transmitted new strain ([Chapter 18](#)). The inflammatory reaction is confined to the superficial squamous mucosa without invasion of the underlying tissue.

Nonspecific atrophic vaginitis may be encountered in postmenopausal women with preexisting atrophy and thinning of the squamous vaginal mucosa.



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## VAGINAL INTRAEPITHELIAL NEOPLASIA AND SQUAMOUS CELL CARCINOMA

Extremely uncommon, these lesions usually occur in women older than age 60 years, with risk factors similar to those for carcinoma of the cervix, discussed below. A preexisting or concurrent cervical intraepithelial neoplasia or carcinoma of the cervix is frequently present. Vaginal intraepithelial neoplasia is a precursor lesion associated with HPV infection in nearly all cases. Invasive squamous cell carcinoma of the vagina is associated with the presence of HPV DNA in more than half of cases.

Of particular interest is vaginal clear cell adenocarcinoma, usually encountered in young women in their late teens to early 20s whose mothers took diethylstilbestrol during pregnancy. Sometimes these cancers do not appear until the third or fourth decade of life. The overall risk is less than 1 per 1000 of those exposed in utero. In about one-third of instances these cancers arise in the cervix. Much more frequently, perhaps in one-third of the population at risk, small glandular or microcystic inclusions appear in the vaginal mucosa. These benign lesions, called *vaginal adenosis*, appear as red granular foci and are lined by mucus-secreting or ciliated columnar cells. It is from such inclusions that the rare clear cell adenocarcinoma arises.





## SARCOMA BOTRYOIDES

Sarcoma botryoides (embryonal rhabdomyosarcoma), producing soft polypoid masses, is another, fortunately rare, form of primary vaginal cancer. It is usually encountered in infants and children younger than the age of 5 years. It may occur in other sites, such as the urinary bladder and bile ducts. These lesions are described in more detail in [Chapter 21](#).







## CERVIX

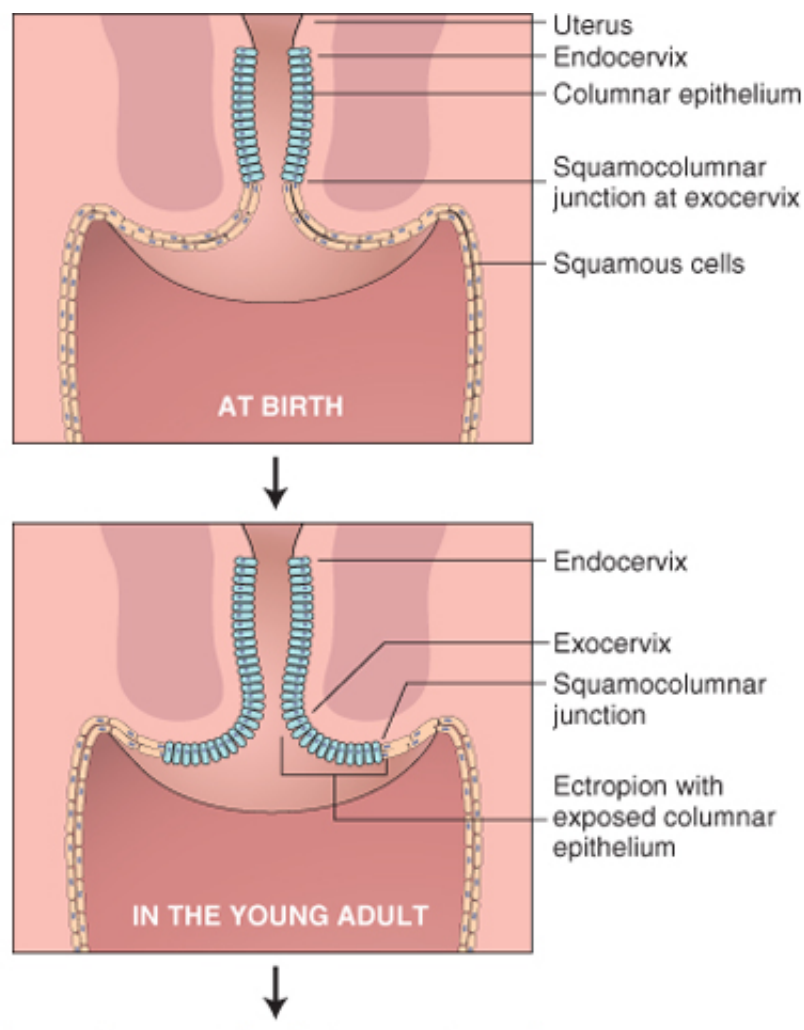
The cervix must serve as a barrier to the ingress of air and the microflora of the normal vaginal tract, yet it must permit the escape of menstrual flow and be capable of dilating to accommodate childbirth. No small wonder it is often the seat of disease. Fortunately, most cervical lesions are relatively banal inflammations (cervicitis), but this is also the site of one of the most common cancers in women; squamous cell carcinoma.

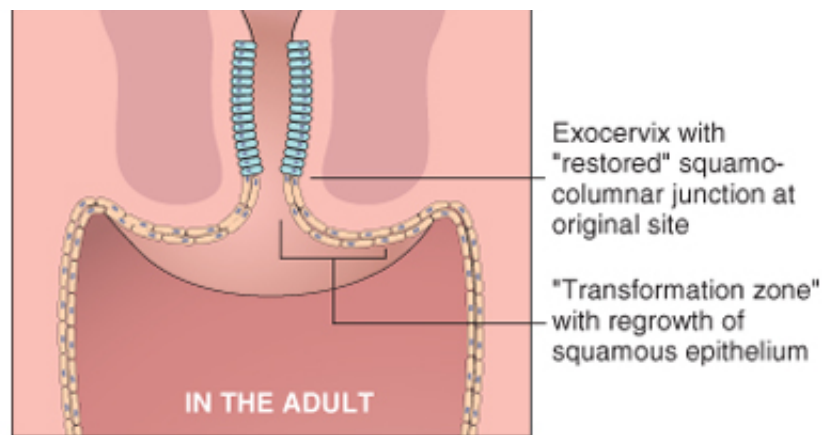


## CERVICITIS

During development, the columnar mucus-secreting epithelium of the endocervix meets the squamous epithelial covering of the exocervix at the external os; thus, the entire "exposed" cervix is covered by squamous epithelium. The endocervical columnar epithelium is not visible to the naked eye or colposcopically. In time, in most young women, there is distal growth of the columnar epithelium that extends beyond the exocervical os, a condition called ectropion; thus, the squamocolumnar junction comes to lie visibly on the exocervix. This "exposed" mucus-secreting columnar epithelium may appear reddened and moist and has mistakenly been called cervical "erosion," but in fact it is the result of normal changes in adult women. Remodeling occurs continuously with regeneration of both squamous and columnar epithelium. The region in which this takes place is known as the *transformation zone* (Fig. 19-5). Frequently, overgrowth of the regenerating squamous epithelium blocks the orifices of endocervical glands in the transformation zone to produce small *nabothian cysts* lined by columnar mucus-secreting epithelium. In the transformation zone, there may be a mild inflammatory infiltrate resulting, possibly, from changes in the vaginal pH or the ever-present microflora of the vagina.

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Figure 19-5 Development of the cervical transformation zone.

Inflammations of the cervix are extremely common and are associated with a mucopurulent to purulent vaginal discharge. Cytologic examination of the discharge reveals white cells and inflammatory atypia of shed epithelial cells, as well as possible microorganisms. These inflammations have been variously subdivided into noninfectious and infectious cervicitis. Because microorganisms are invariably present in the vagina, with or without associated inflammatory changes on cytologic examination, it is difficult to differentiate noninfectious from infectious cervicitis. Often present are indigenous and, for the most part, incidental vaginal aerobes and anaerobes, streptococci, staphylococci, enterococci, and *Escherichia coli*. Much more important are *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *T. vaginalis*, *Candida* spp., *Neisseria gonorrhoeae*, herpes simplex II (genitalis), and one or more types of HPV. Many of these microorganisms are transmitted sexually, and so the cervicitis may represent a sexually transmitted disease. Among these pathogens, *C. trachomatis* is by far the most common and accounts for as many as 40% of cases of cervicitis encountered in sexually transmitted disease clinics, thus being far more common than gonorrhea. Herpetic infections of the cervix are noteworthy, because this organism may be transmitted to the infant during passage through the birth canal, sometimes resulting in a serious, sometimes fatal, systemic herpetic infection (Chapter 7).

### Morphology

Nonspecific cervicitis may be either **acute** or **chronic**. Excluding gonococcal infection, which causes a specific form of acute disease, the relatively uncommon **acute nonspecific form** is limited to postpartum women and is usually caused by staphylococci or streptococci. The chronic form is a nearly ubiquitous entity usually referred to as **nonspecific cervicitis**.

Specific forms include herpesvirus ulcerative lesions and changes caused by *C. trachomatis*. Chronic cervicitis is not easily defined, but it consists of inflammation and epithelial regeneration common in all women of reproductive age. The cervical epithelium may show hyperplasia and reactive changes. These changes may occur in both squamous and columnar mucosa. Eventually, columnar epithelium undergoes squamous metaplasia or transformation into a stratified squamous epithelium.

Cervicitis commonly comes to attention on routine examination or because of marked leukorrhea. Culture of the discharge must be interpreted cautiously, because commensal organisms are virtually always present. Only the identification of known pathogens is helpful. When the lesion is severe, inflammatory changes can make differentiation from carcinoma

When the lesion is severe, inflammatory changes can make differentiation from carcinoma difficult on cytologic preparations and even with colposcopy. Differentiation of inflammatory changes from premalignant dysplasia may also be difficult on cervical biopsy specimen.



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## TUMORS OF THE CERVIX

Despite dramatic improvements in early diagnosis and treatment, cervical carcinoma continues to be a leading cause of related deaths in women, particularly in the developing world. The only other "tumor" meriting mention is

### **Cervical Intraepithelial Neoplasia (CIN) and Squamous Cell Carcinoma**

Cervical carcinoma was once the most frequent form of cancer in women around the world. Since the introduction of the (Pap) smear 50 years ago, the incidence of cervical cancer has plummeted. The Pap smear remains the most effective test ever developed. In populations that are screened regularly, cervical cancer mortality is reduced. In the United States, Pap screening has dramatically lowered the incidence of invasive cervical tumors to about 10 cases per year, with mortality to about 3900 cases per year, ranking it 13th in cancer deaths for women. Many of the cases are now found in women who have not had regular screening. Over the same period the incidence of precursor CIN (attributable to better case finding) to its present level of more than 50,000 cases annually. This growth is due to the early detection of precursor lesions by the Pap smear at an early stage, permitting discovery of these lesions before they become invasive.

It is important to emphasize here that nearly all invasive cervical squamous cell carcinomas arise from precursor lesions referred to as CIN. However, not all cases of CIN progress to invasive cancer, and indeed many patients with CIN will be pointed out.

### **Cervical Intraepithelial Neoplasia**

Cytologic examination can detect CIN long before any abnormality can be seen grossly. The following precancerous epithelial changes (CIN) may precede the development of an overt cancer by many years. However, as noted earlier, only a fraction of cases of CIN progress to invasive carcinoma. The process may begin as low-grade CIN and progress to higher grade CIN, or they may begin at the outset as high-grade CIN. The location of the HPV infection in the transformation zone, the type of HPV infection (high versus low risk), and host factors. On the basis of histology, precancerous changes are graded as follows:

CIN I: Mild dysplasia  
CIN II: Moderate dysplasia  
CIN III: Severe dysplasia and carcinoma in situ

However, in cytologic smears, the current Bethesda system separates the precancerous lesions into low-grade squamous intraepithelial lesions (LSIL). The low-grade lesions correspond to CIN I or flat condylomas. High-grade lesions to CIN II or III. Progression from a lower grade to a higher grade is not inevitable. At least 50% to 60% of low-grade lesions regress, that of persistence is 30%, and that of progression to CIN III is 5%. With CIN III the likelihood of regression is only 33% and of progression to invasive cancer 60%. That the higher the grade of CIN, the greater the likelihood of progression, but it should be noted that not all lesions do not progress to cancer.

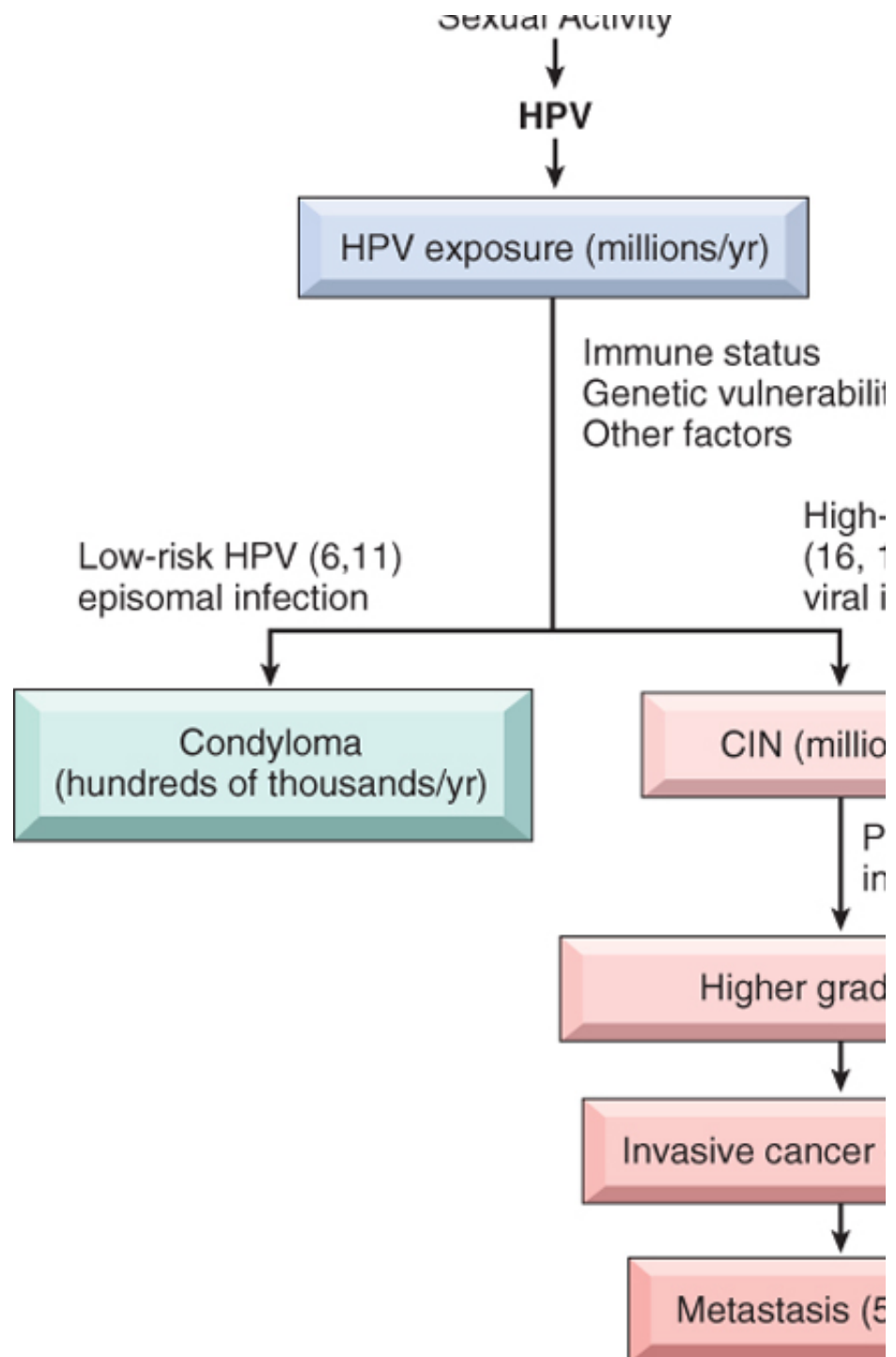
### **Epidemiology and Pathogenesis**

The peak age incidence of CIN is about 30 years, whereas that of invasive carcinoma is about 45 years. CIN is occasionally seen in women in their early 20s, precancerous changes usually take many years, particularly in the case of invasive carcinomas.

Important risk factors for the development of CIN and invasive carcinoma are:

Early age at first intercourse  
Multiple sexual partners  
A male partner with multiple previous sexual partners  
"high-risk" papillomaviruses.

Sexual Activity



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 Figure 19-6 An attempt to depict the sequence of events that may follow human papillomavirus (HPV) infection

Many other risk factors can be related to these four, including the higher incidence in lower socioeconomic groups and the association with multiple pregnancies. They point to the likelihood of sexual transmission. Indeed, HPV can be detected by molecular methods in nearly all precancerous lesions and invasive cancers. High-risk HPV types, including 16, 18, 45, and 31, account for the majority of cervical carcinomas, while low-risk types, including 6, 11, 42, and 44, are associated with condylomas (Fig. 19-6). In these benign lesions the viral DNA does not integrate into the host genome and express large amounts of viral proteins. By contrast, HPV types 16 and 18 usually integrate into the host genome and express large

block or inactivate tumor suppressor genes *p53* and *RB*, respectively (Chapter 6). The result is a cell with autonomous growth and susceptible to the acquisition of further mutations. The recently introduced HPV vaccines are preventing HPV infections and hence cervical cancers.

Although many women harbor these viruses, only a few develop cancer, suggesting other influential factors. Defined risk factors are cigarette smoking and exogenous or endogenous immunodeficiency. For example, cervical cancer *in situ* is increased approximately fivefold in women infected with human immunodeficiency virus who are also infected with HPV.

### Morphology

The cervical epithelial changes included within the term **CIN** begin with mild dysplasia called **condyloma**. This lesion is characterized by koilocytotic changes mostly in the superficial layers of the epithelium. **Koilocytosis**, as you will recall from the earlier discussion of condyloma, is characterized by cells composed of nuclear hyperchromasia and angulation with perinuclear vacuolization, a characteristic effect of HPV. In CIN II the dysplasia is more severe, with maturation of keratinocytes in the superficial third of the epithelium. It is associated with some variation in cell and nuclear size, increased mitoses above the basal layer, extending in to the middle third of the epithelium. The superficial layer of cells shows some differentiation, and in some cases it shows the changes described. The next level of dysplasia, not always distinct from CIN II, is CIN III, marked by marked variation in cell and nuclear size, marked chromatin heterogeneity, disorderly orientation, and normal or abnormal mitoses; these changes affect virtually all layers of the epithelium by loss of maturation. Differentiation of surface cells and koilocytotic changes have been described (Figs. 19-7 and 19-8). CIN II and III may begin as CIN I or arise *de novo*, depending on the HPV type. In time, dysplastic changes become more atypical and may extend into the deeper layers, but **the alterations are confined to the epithelial layer and its glands**. These changes are called **carcinoma in situ**. The next stage, if it is to appear, is invasive cancer. However, there is no inevitability to this progression.

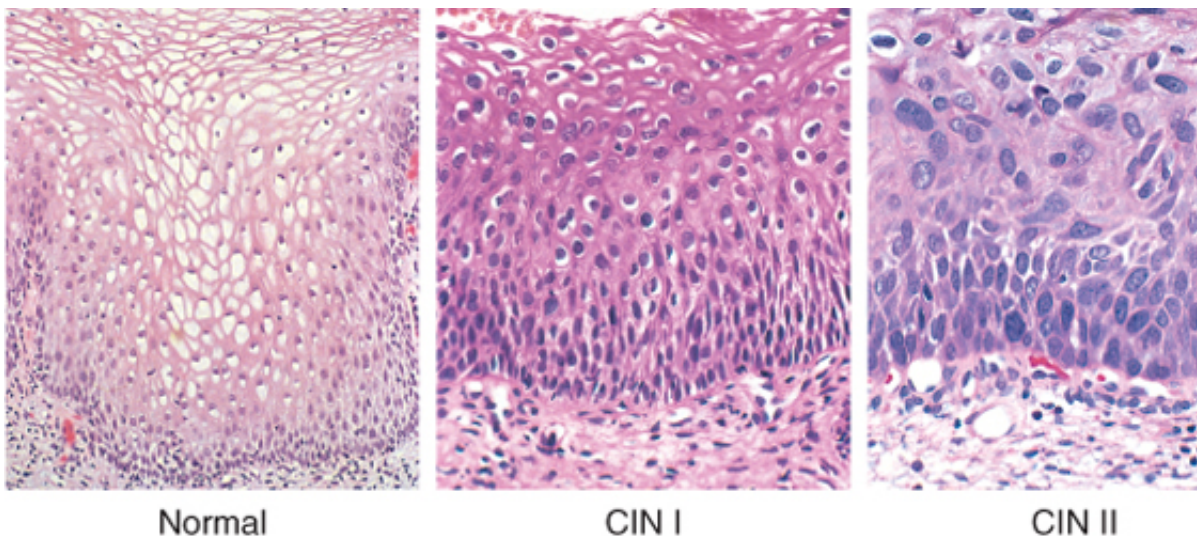
Cervical precancers produce cytologic abnormalities that often (but not always) reflect the severity of the lesion. More than 70% of CINs of all grades are associated with "high-risk" HPVs. Moreover, as many as one-half of the women with cytologic abnormalities (e.g., atypical squamous cells of undetermined significance) may be associated with HPV. These changes will be followed by a biopsy-proven CIN II or CIN III. Among women with cytologic abnormalities associated with high-risk HPVs, approximately 10% will eventually develop a high-grade CIN.

Although HPV testing can identify the pool of women at risk for cervical cancer, most sexually active women have HPV infections at some point in their lifetime. This limits the usefulness of HPV testing as a screening tool. Cytology and cervical examinations (colposcopy) remain the mainstays of cervical cancer prevention. Negative results with the use of molecular probes for HPV DNA are *at extremely low risk for harboring a high-grade CIN*. New screening methods for this group are being formulated.

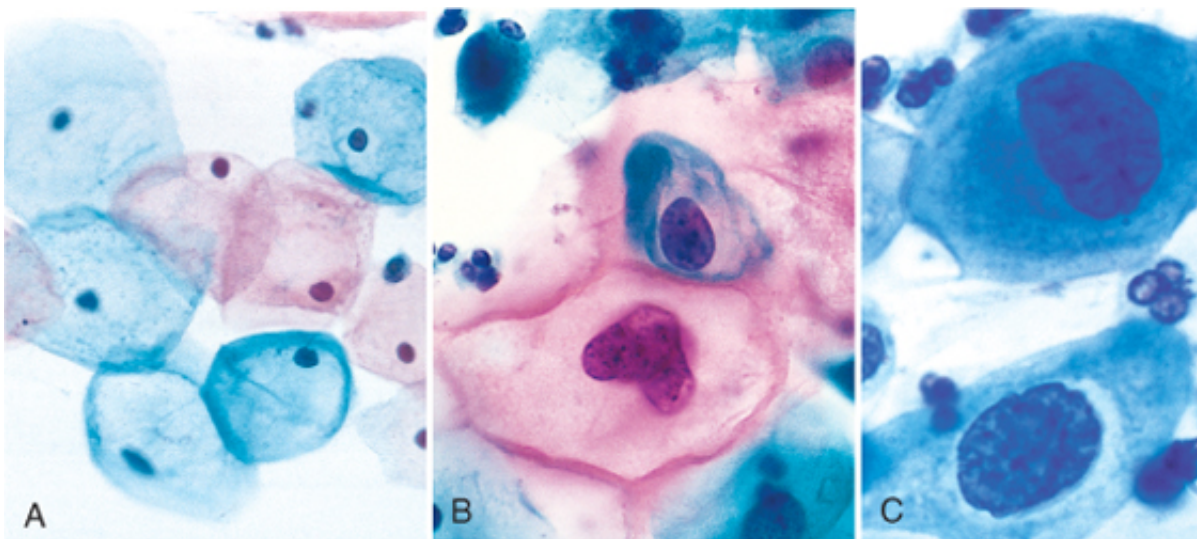
### Invasive Carcinoma of the Cervix

The importance of cervical cancer as a cause of morbidity and mortality around the world, particularly in developing countries, has been emphasized. The most common cervical carcinomas are squamous cell carcinomas (75%), adenosquamous carcinomas (20%), and small-cell neuroendocrine carcinomas (<5%). The squamous cell carcinoma is appearing in younger women, now with a peak incidence at about 45 years, some 10 to 15 years earlier than in the past. In some individuals with particularly aggressive intraepithelial changes, the time interval may be even shorter. In women CIN precursors may persist for life. Many variables, both constitutional and acquired, modify the course of the disease and are monitored with careful follow-up and repeat biopsies. The relative proportion of squamous and glandular lesions is increasing in recent decades; glandular lesions are not detected well by Pap smear and other screening methods. Squamous carcinoma is becoming less frequent.

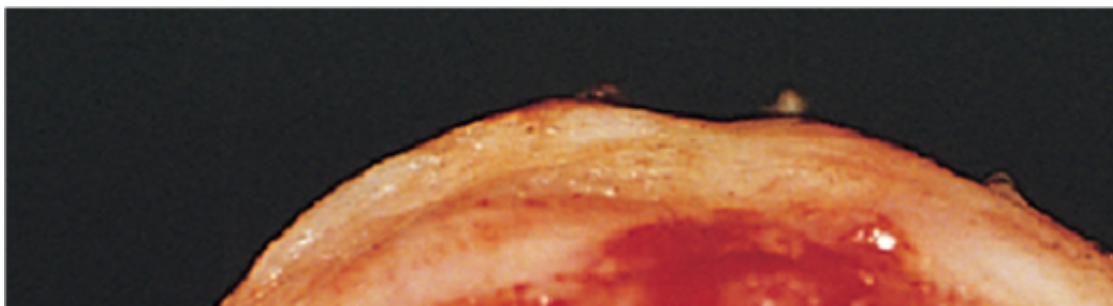




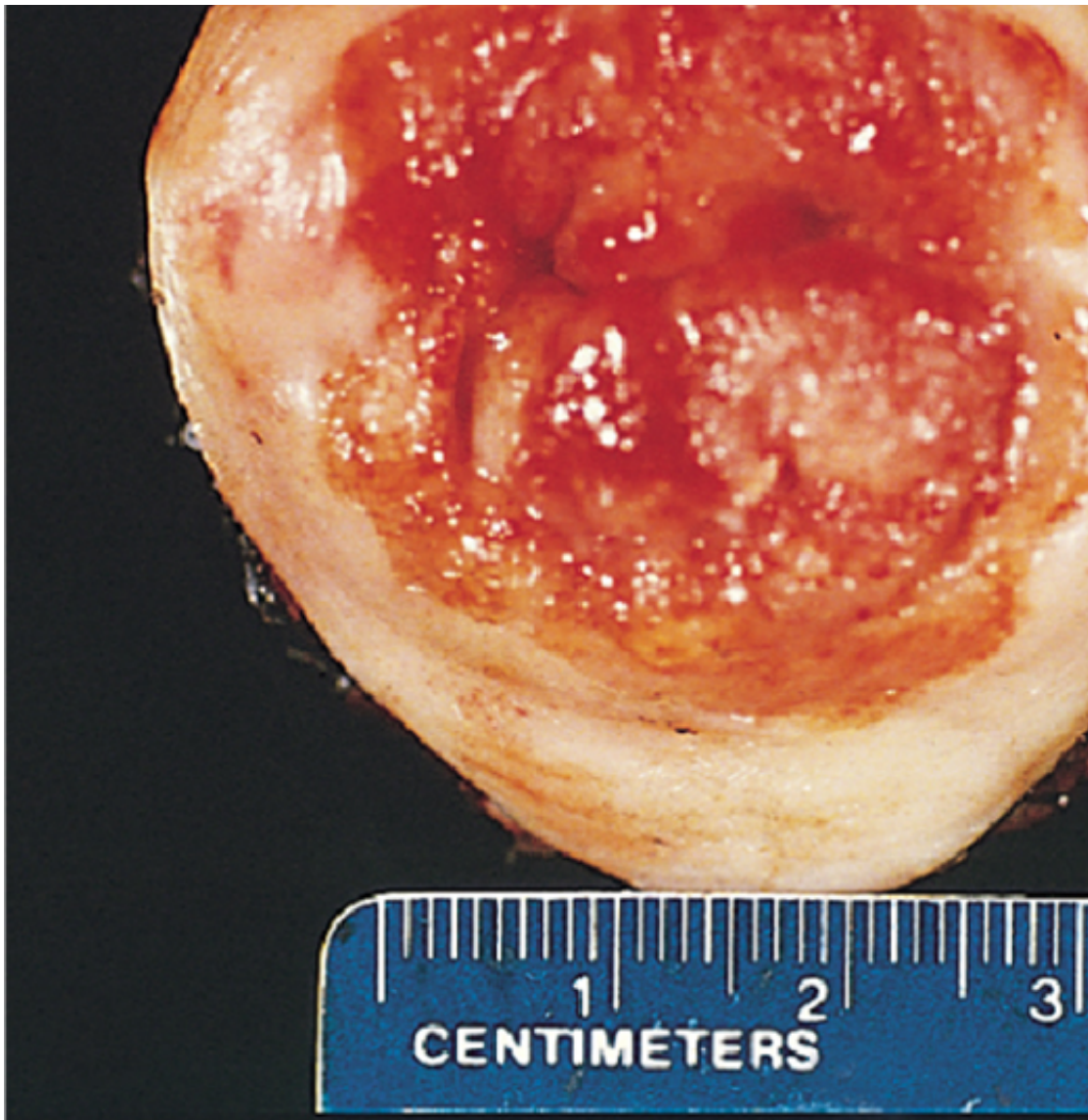
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 Figure 19-7 Spectrum of CIN: normal squamous epithelium for comparison; CIN I with koilocytotic atypia; CIN II (carcinoma in situ) with diffuse atypia and loss of maturation.



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 Figure 19-8 The cytology of CIN as seen on the Papanicolaou smear. **A-B**, Cytoplasmic staining in superficial cells. **B**, CIN I. **C**, CIN II. **D**, CIN III. Note the reduction in cytoplasm and the increase in nuclear size as the lesion increases. This reflects the progressive loss of cellular differentiation on the surface of the cervical epithelium (see [Figure 19-7](#)). (Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston.)







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Figure 19-9 Carcinoma of the cervix, well advanced.

### **Morphology**

Invasive carcinomas of the cervix develop in the region of the transformation zone. Microscopic foci of early stromal invasion to grossly conspicuous tumors encircling the cervix may be invisible or exophytic. Tumors encircling the cervix and penetrating the stroma produce a "barrel cervix," which can be identified by direct palpation. Extensive soft tissue fixation can fix the uterus to the pelvic structures. Spread to pelvic lymph nodes, depth and the presence of capillary-lymphatic invasion, ranging from less than 1% depth to over 10% once invasion exceeds 5 mm. Distant metastases, including paraneoplastic involvement, remote organ involvement, or invasion of adjacent structures such as the lungs, are late in the course of disease. With the exception of neuroendocrine tumors, which have a different behavior, cervical carcinomas are graded from 1 to 3 based on cellular differentiation and from 1 to 4 depending on clinical spread.

### **Clinical Course**

With the advent of the Pap smear, an increasing proportion of cervical carcinomas are diagnosed at an early stage.

majority of cervical neoplasms are diagnosed in the preinvasive phase and appear as white areas on application of dilute [acetic acid](#)<sup>®</sup>. More advanced cases of cervical cancer are invariably seen in a recent smear or have waited many years since the prior smear. Such tumors may be symptomatic, called leukorrhea, painful coitus (dyspareunia), and dysuria. Mortality is most strongly related to the type of tumor (e.g., squamous cell carcinoma vs. adenocarcinoma vs. neuroendocrine tumors) to cell type. Detection of precursors by cytologic examination and their eradication by conization or hysterectomy is the most effective method of cancer prevention. However, once cancer develops, the overall survival is poor. The 5-year survival rates are as follows: stage 0 (preinvasive), 100%; stage 1, 90%; stage 2, 82%; stage 3, 35%; and stage 4, 17%. The 5-year survival of women even with positive pelvic nodes approaches 50%. Chemotherapy and radiation therapy may be used in advanced cases.

## SUMMARY

### Cervical Neoplasia

Risk factors for cervical carcinoma include early age at first intercourse, multiple sexual partners, cigarette smoking, immunodeficiency, and infection by "high-risk" papilloma virus. Cervical carcinoma is HPV related, particularly certain HPV subtypes (16, 18, 45, 31, 33, 35, 39, 42, 51, 52, 56, 58, 59, 68, 73, 82, 84, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 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2215, 2216, 2217, 2218, 2219, 2220, 2221, 222



## BODY OF UTERUS

The uterine corpus with its lining endometrium is the principal seat of female reproductive tract disease. Many disorders of this organ are common, often chronic and recurrent, and sometimes disastrous. Only the more frequent and significant ones are considered here.





## ENDOMETRITIS

Inflammation of the endometrium is seen as part of the wider spectrum of pelvic inflammatory disease, a condition with consequences for the integrity of the fallopian tubes and subsequent fertility, as discussed below. Endometritis may be associated with retained products of conception subsequent to miscarriage or delivery, or a foreign body such as an intrauterine device. Retained tissue or foreign bodies act as a nidus for infection, frequently by flora ascending from the vaginal and intestinal tract, and removal of the offending tissue or foreign body typically results in resolution.

Endometritis is classified as acute or chronic based on whether there is a predominant neutrophilic or lymphoplasmacytic response; however, components of both may be present in a given uterus. Generally the diagnosis of chronic endometritis requires the presence of plasma cells. Acute endometritis is frequently due to *N. gonorrhoeae* or *C. trachomatis*. Histologically, neutrophilic infiltrate in the superficial endometrium and glands coexists with a stromal lymphoplasmacytic infiltrate. Prominent lymphoid follicles are more commonly seen in chlamydial infection. By contrast, *Mycoplasma* infection has a subtle lymphocytic stromal infiltrate. All forms of endometritis may present with fever, abdominal pain, menstrual abnormalities, infertility and ectopic pregnancy due to damage to the fallopian tubes (see below).

Occasionally tuberculosis may present with a granulomatous endometritis, frequently with tuberculous salpingitis and peritonitis. Although seen in the United States mainly in immunocompromised individuals, it is common in other countries where tuberculosis is endemic and should receive consideration in the differential diagnosis of pelvic inflammatory disease in women who have recently emigrated from endemic areas.







## ADENOMYOSIS

Adenomyosis refers to the growth of the basal layer of the endometrium down into the myometrium. Nests of endometrial stroma, glands, or both, are found well down in the myometrium between the muscle bundles. In the fortuitous microscopic section, continuity between these nests and the overlying endometrium can be established. The uterine wall often becomes thickened and the uterus is enlarged and globular as a result of the presence of endometrial tissue and a reactive hypertrophy of the myometrium. Because these glands derive from the stratum basalis of the endometrium, they do not undergo cyclical bleeding. Nevertheless, marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation.



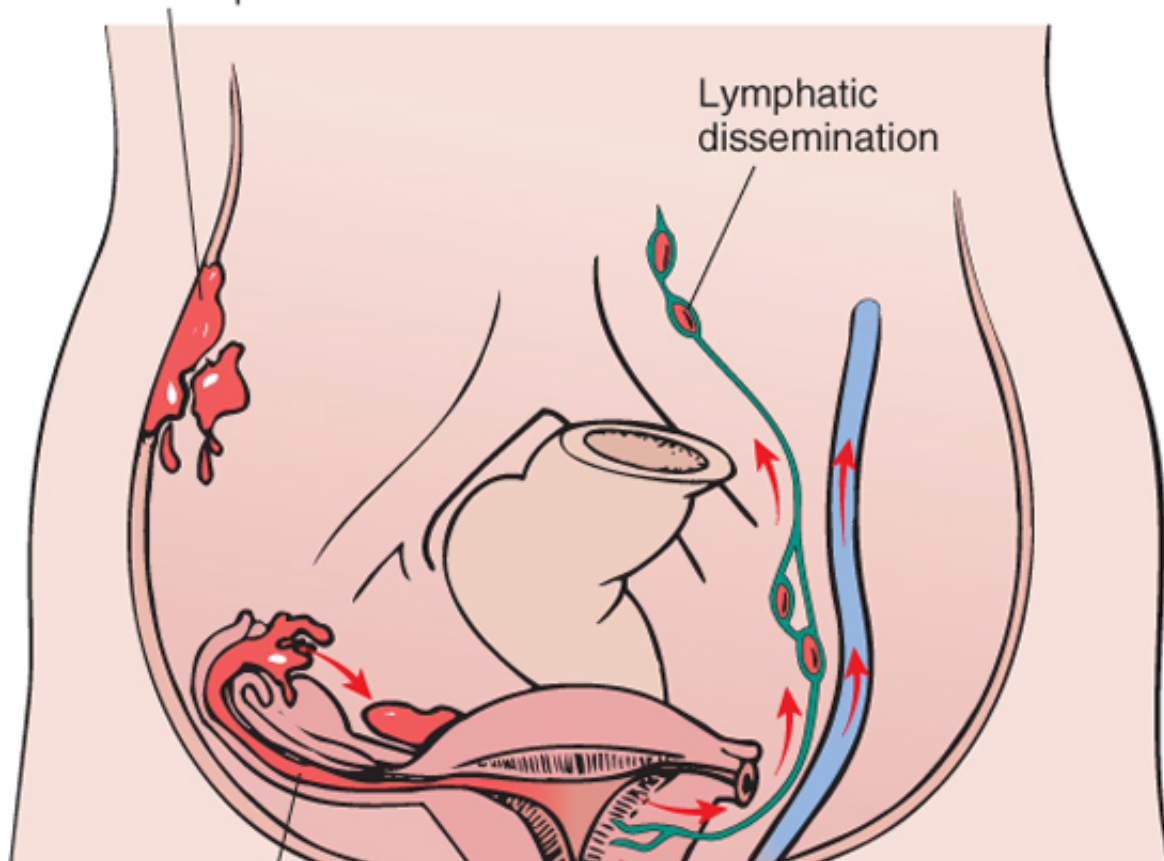


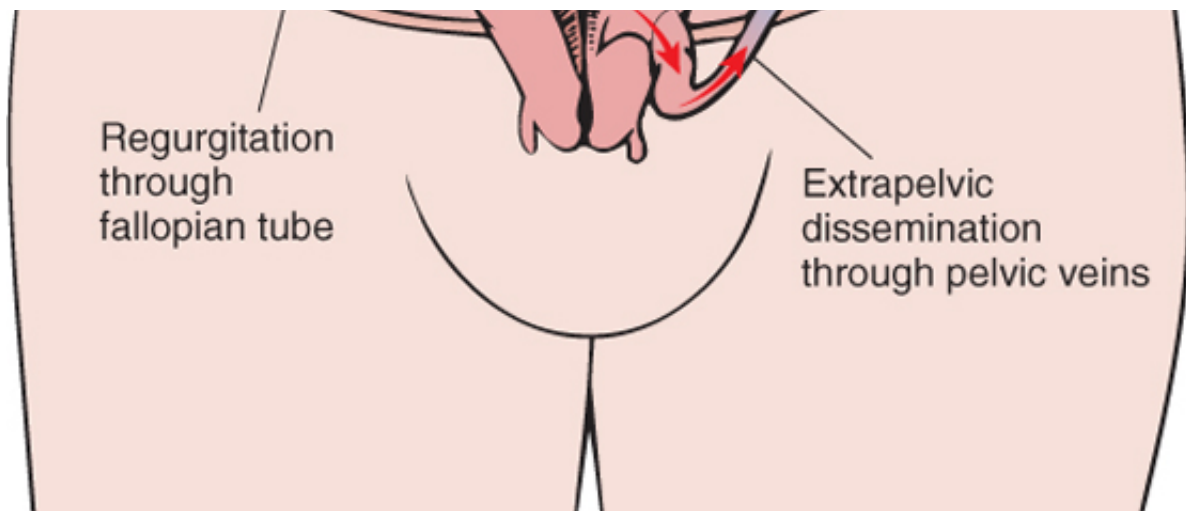
## ENDOMETRIOSIS

Endometriosis is characterized by endometrial glands and stroma in a location outside the endomyometrium. It occurs in as many as 10% of women in their reproductive years and in nearly half of women with infertility. It is a common cause of dysmenorrhea, and pelvic pain, and may present as a pelvic mass filled with degenerating blood (chocolate cyst). It is frequently multifocal and may involve tissue in the pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum), less frequently in more remote sites of the peritoneal cavity and about the umbilicus and uncommonly lymph nodes, lungs, and even heart, skeletal muscle, or bone.

Three possibilities (not mutually exclusive) have been invoked to explain the origin of these dispersed lesions (Fig. 19-10). First, the *regurgitation theory*, currently the most accepted, proposes menstrual backflow through the fallopian tubes with subsequent implantation. Indeed, menstrual endometrium is viable and survives when injected into the anterior abdominal wall; however, this theory cannot explain lesions in the lymph nodes, skeletal muscle, or lungs. Second, the *metaplastic theory* proposes endometrial differentiation of coelomic epithelium, which is the origin of the endometrium itself. This theory, too, cannot explain endometriotic lesions in the lungs or lymph nodes. Third, the *vascular or lymphatic dissemination theory* has been invoked to explain extrapelvic or intranodal implants. Conceivably, all pathways are valid in individual instances.

### Metaplastic differentiation of coelomic epithelium





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Figure 19-10 The potential origins of endometrial implants.

### Morphology

In contrast to adenomyosis, **endometriosis** almost always contains **functioning endometrium**, which undergoes cyclic bleeding. Because blood collects in these aberrant foci, they usually appear grossly as red-blue to yellow-brown nodules or implants. They vary in size from microscopic to 1 to 2 cm in diameter and lie on or just under the affected serosal surface. Often individual lesions coalesce to form larger masses. When the ovaries are involved, the lesions may form large, blood-filled cysts that are transformed into so-called **chocolate cysts** as the blood ages (Fig. 19-11). Seepage and organization of the blood leads to widespread fibrosis, adherence of pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries. The histologic diagnosis at all sites depends on finding two of the following three features within the lesions: endometrial glands, stroma, or hemosiderin pigment.

The clinical manifestations of endometriosis depend on the distribution of the lesions. Extensive scarring of the oviducts and ovaries often produces discomfort in the lower abdominal quadrants and eventually causes sterility. Pain on defecation reflects rectal wall involvement, and dyspareunia (painful intercourse) and dysuria reflect involvement of the uterine and bladder serosa, respectively. In almost all cases, there is severe dysmenorrhea and pelvic pain as a result of intrapelvic bleeding and periuterine adhesions.





## DYSFUNCTIONAL UTERINE BLEEDING AND ENDOMETRIAL HYPERPLASIA



Figure 19-11 This ovary has been sectioned to reveal a large endometriotic cyst with degenerated blood ("chocolate" cyst).

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By far the most common problem for which women seek medical attention is some disturbance in menstrual function: *menorrhagia* (profuse or prolonged bleeding at the time of the period), *metrorrhagia* (irregular bleeding between the periods), *ovulatory* (intermenstrual) or *postmenopausal* bleeding. Common causes include polyps, leiomyomas, endometrial carcinoma, endometrial hyperplasia, and endometritis. Vaginal bleeding may also be due to lesions of the cervix and vagina, such as polyps, cervicitis, or carcinoma.

### Dysfunctional Uterine Bleeding

Abnormal bleeding in the absence of a well-defined organic lesion in the uterus is called dysfunctional uterine bleeding. The probable cause of abnormal uterine bleeding, dysfunctional or organic (related to a well-defined lesion), depends somewhat on the age of the woman ([Table 19-1](#)).

The various causes of dysfunctional bleeding can be segregated into four groups:

*Failure of ovulation.* Anovulatory cycles are very common at both ends of reproductive life; with any dysfunction of the hypothalamic-pituitary axis, adrenal, or thyroid; with a functioning ovarian lesion producing an excess of estrogen; with malnutrition, obesity, or debilitating disease; and with severe physical or emotional stress. Regardless of the basis for the failure of ovulation, it leads to an excess of estrogen relative to [progesterone<sup>®</sup>](#). Thus, the endometrium goes through a proliferative phase that is not followed by the normal secretory phase. The endometrial glands may develop mild cystic changes or in other places may appear disorderly with a relative scarcity of stroma, which requires [progesterone<sup>®</sup>](#) for its support. The poorly supported endometrium partially collapses, with rupture of spiral arteries, accounting for the bleeding. *Inadequate luteal phase.* The corpus luteum may fail to mature normally or may regress prematurely, leading to a relative lack of [progesterone<sup>®</sup>](#). The endometrium under these circumstances reveals delay in the development of the secretory changes expected at the date of biopsy. *Contraceptive-induced bleeding.* Older oral contraceptives containing synthetic estrogens and progestin induced a variety of endometrial responses—for example, a lush, decidua-like stroma and inactive, nonsecretory glands. The pills in current use have corrected these abnormalities. *Endomyometrial disorders*, including chronic endometritis, endometrial polyps, and submucosal leiomyomas.

**Table 19-1. Causes of Abnormal Uterine Bleeding by Age Group**

Age Group	Cause(s)
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)



age	Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)
	Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopause	Anovulatory cycle Irregular shedding Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopause	Organic lesions (carcinoma, hyperplasia, polyps) Endometrial atrophy

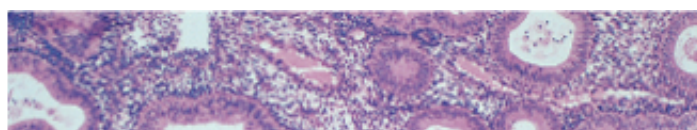
## Endometrial Hyperplasia

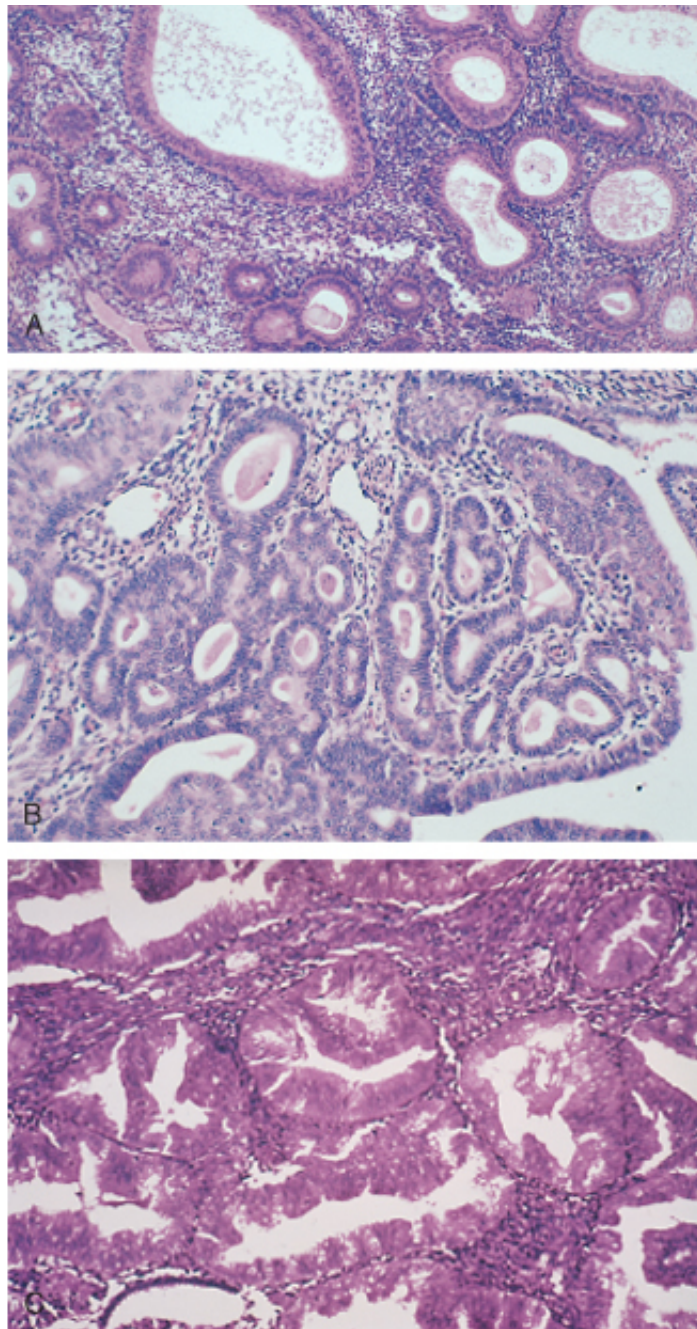
An excess of estrogen relative to progesterin, if sufficiently prolonged or marked, will induce exaggerated endometrial proliferation (hyperplasia), which can be preneoplastic. The severity of hyperplasia is classified based on architectural crowding and cytologic atypia, ranging from simple hyperplasia to complex hyperplasia, and finally atypical hyperplasia (Fig. 19-12). These three categories represent a continuum based on the level and duration of the estrogen excess. Not surprisingly, in time the hyperplasia may become autonomously proliferating, no longer needing estrogenic influence, eventually giving rise to carcinoma. The risk of developing carcinoma is dependent on the severity of the hyperplastic changes and associated cellular atypia. Simple hyperplasia carries a negligible risk, while a person with atypical hyperplasia with cellular atypia has a 20% risk of developing endometrial carcinoma. Any estrogen excess may lead to hyperplasia. Potential contributors include failure of ovulation, such as is seen around the menopause; prolonged administration of estrogenic steroids without counterbalancing progesterin; estrogen-producing ovarian lesions such as polycystic ovaries (including Stein-Leventhal syndrome); cortical stromal hyperplasia; and granulosa-theca cell tumors of the ovary. A common risk factor is obesity, because adipose tissue processes steroid precursors into estrogens. When atypical hyperplasia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by repeated endometrial biopsy.

## SUMMARY

### Non-neoplastic Disorders of Endometrium

Endometriosis refers to location of endometrial glands and stroma outside the uterus and may involve the pelvic or abdominal peritoneum, and sometimes distant sites like lymph nodes and lungs. The ectopic endometrium in endometriosis undergoes cyclical bleeding and is a common cause of dysmenorrhea and pelvic pain. Adenomyosis refers to growth of endometrium into the myometrium with uterine enlargement. Unlike endometriosis there is no cyclical bleeding. Endometrial hyperplasia results from an excess of estrogen, whether endogenous or exogenous. Risk factors for developing hyperplasia include anovulatory cycles, polycystic ovary syndrome, estrogen-producing ovarian tumor, obesity, and hormone intake. The severity of hyperplasia is graded by architectural and cytologic criteria. Complex architecture associated with cytologic atypia has a 20% risk of developing carcinoma.





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 Figure 19-12 **A**, Anovulatory or "disordered" endometrium with dilatation of glands. **B**, Complex hyperplasia displaying a nest of closely packed glands. **C**, Atypical endometrial hyperplasia with crowding of glands, unfolding of tall columnar cells, and some loss of polarity.





## TUMORS OF THE ENDOMETRIUM AND MYOMETRIUM

The most common neoplasms of the body of the uterus are endometrial polyps, smooth muscle tumors, and leiomyomas. They tend to produce bleeding from the uterus as the earliest manifestation.

### Endometrial Polyps

These are sessile, usually hemispheric (rarely pedunculated) lesions that are 0.5 to 3 cm in diameter. They protrude into the endometrial mucosa into the uterine cavity. Histologically they are composed of endometrial stroma and muscular arteries. Some have an essentially normal endometrial architecture, but more often they lack normal architecture. Stromal cells in most endometrial polyps are monoclonal and have a cytogenetic rearrangement and a neoplastic component of the polyp.

Although endometrial polyps may occur at any age, they develop more commonly at the time of menopause. They are associated with the production of abnormal uterine bleeding and, more important, the risk (however rare) of giving rise to endometrial adenocarcinoma.

### Leiomyoma and Leiomyosarcoma

Benign tumors that arise from the smooth muscle cells in the myometrium are properly termed *leiomyomas*. If malignant, they are more often referred to as *fibroids*. They are the most common benign tumor in female women during reproductive life. Some genetic influence may be involved; these tumors are consistently monoclonal. Estrogens and possibly oral contraceptives stimulate their growth; conversely, they shrink after menopause. Clearly monoclonal, and nonrandom chromosomal abnormalities have been found in about 40% of leiomyomas.

#### Morphology

Macroscopically leiomyomas are typically **sharply circumscribed**, firm gray-white nodules with a characteristic **whorled cut surface**. They may occur singly, but most often multiple within the uterus, ranging in size from small seedlings to massive neoplasms that compress the endometrium (Fig. 19-13). Some are embedded within the myometrium (intramural), whereas others are located beneath the endometrium (submucosal) or directly beneath the serosa (subserosal). They may have attenuated stalks and even become attached to surrounding organs, from which they may detach and then free themselves from the uterus to become "parasitic" leiomyomas. Large leiomyomas may have foci of ischemic necrosis with areas of hemorrhage and cystic softening, and after menopause they may become densely collagenous and even calcified. Histologically, the tumors are characterized by **bundles of smooth muscle cells** duplicating the histology of the normal myometrium. Calcification, ischemic necrosis, cystic degeneration, and hemorrhage may be present.







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Figure 19-13 Multiple leiomyomas of the uterus. Several large, almost pedunculated tumors protrude from the fundus of the uterus. The cervix is below (on top of white bar). (Courtesy of Dr. Kyle Molberg, Department of Pathology, University of Texas)

*Leiomyomas* of the uterus may be entirely asymptomatic and be discovered only on routine pelvic examination. When present, the frequent manifestation is menorrhagia, with or without metrorrhagia. Large masses are palpable to the woman or may produce a dragging sensation. Benign leiomyomas rarely transform. The presence of multiple lesions does not increase the risk of harboring a malignancy.

*Leiomyosarcomas* typically arise *de novo* from the mesenchymal cells of the myometrium, not from leiomyomas. They are almost always solitary tumors, in contradistinction to the frequently multiple leiomyomas.

### **Morphology**

Grossly, leiomyosarcomas develop in several distinct patterns: as bulky masses in the myometrium, as polypoid lesions projecting into the uterine cavity, or as deceptively discrete tumors that resemble large, benign leiomyomas. They are frequently soft, hemorrhagic, and necrotic. Within this wide range of differentiation, from those that closely resemble leiomyoma to wildly different, it is understandable that some well-differentiated tumors are difficult to distinguish between benign and malignant, and sometimes these are designated as smooth muscle tumors of uncertain malignant potential. The diagnostic features of leiomyosarcoma include tumor necrosis, increased mitotic activity, and the degenerative necrosis frequently seen in leiomyomas, cytologic atypia, and mitotic activity. Increased mitotic activity alone is sometimes seen in benign smooth muscle tumors; therefore, assessment of all three features is necessary to make a diagnosis of malignancy.

Recurrence after removal is common with these cancers, and many metastasize, typically to the lungs. The overall survival is about 40%. Understandably, the more anaplastic tumors have a poorer outlook than the better differentiated ones.

### **SUMMARY**

#### **Uterine Smooth Muscle Neoplasms**

Benign smooth muscle tumors, called leiomyomas, are common and frequently present as menorrhagia, as a pelvic mass, or as a cause of infertility. Malignant smooth muscle tumors, called leiomyosarcomas, seem to arise *de novo*; multiple benign leiomyomas do not increase the risk of malignancy. Criteria of malignancy include necrosis, increased mitotic activity, and cytologic atypia.



not increase the risk of malignancy. Criteria of malignancy include necrosis, mitotic activity.

## Endometrial Carcinoma

In the United States and many other Western countries, endometrial carcinoma is the most frequent gynecologic cancer. Some years ago, it was much less common than cervical cancer. However, early detection and its appropriate treatment have dramatically reduced the incidence of invasive cervical cancer.

### *Epidemiology and Pathogenesis*

Endometrial cancer appears most frequently between the ages of 55 and 65 years and is distinctly related to the years of age. There are two clinical settings in which endometrial carcinomas arise: in perimenopausal women with endometrial atrophy. These scenarios are correlated with differences in histology of the endometrium, respectively.

There is a constellation of well-defined risk factors for endometrioid carcinoma:

Obesity: increased synthesis of estrogens in fat depots and from adrenal and ovarian precursors. Nulliparous women tend to be nulliparous, often with nonovulatory cycles.

These risk factors point to *increased estrogen stimulation*, and indeed it is well recognized that progestins and estrogen-secreting ovarian tumors increase the risk of this form of cancer. The great preponderance is in the setting just described. Many of these risk factors are the same as those for endometrial hyperplasia. These tumors are termed *endometrioid* and frequently arise on a background of endometrial hyperplasia. These tumors are termed *endometrioid* endometrial glands. Breast carcinoma occurs in women with endometrial cancer (and vice versa).

Dissecting the pathogenesis of endometrioid carcinoma is aided by analysis of two familial cancer syndromes of the endometrioid type of endometrial carcinoma:

Endometrial carcinoma is the second most common cancer associated with *hereditary non-polyposis colorectal cancer* (HNPCC). Sporadic cases of endometrioid-type carcinoma show a high frequency of inactivation of these genes by methylation of the promoter, and as a consequence, microsatellite instability. Persons with *Cowden's syndrome*, a multiple hamartoma syndrome, have a high risk of carcinoma of the breast, thyroid, and endometrium, have mutations in *PTEN*, a tumor suppressor gene. Endometrioid carcinoma also harbor mutations in *PTEN*. In fact, both mismatch repair genes are involved in endometrial carcinogenesis, occurring in the progression from abnormal proliferation to atypia.

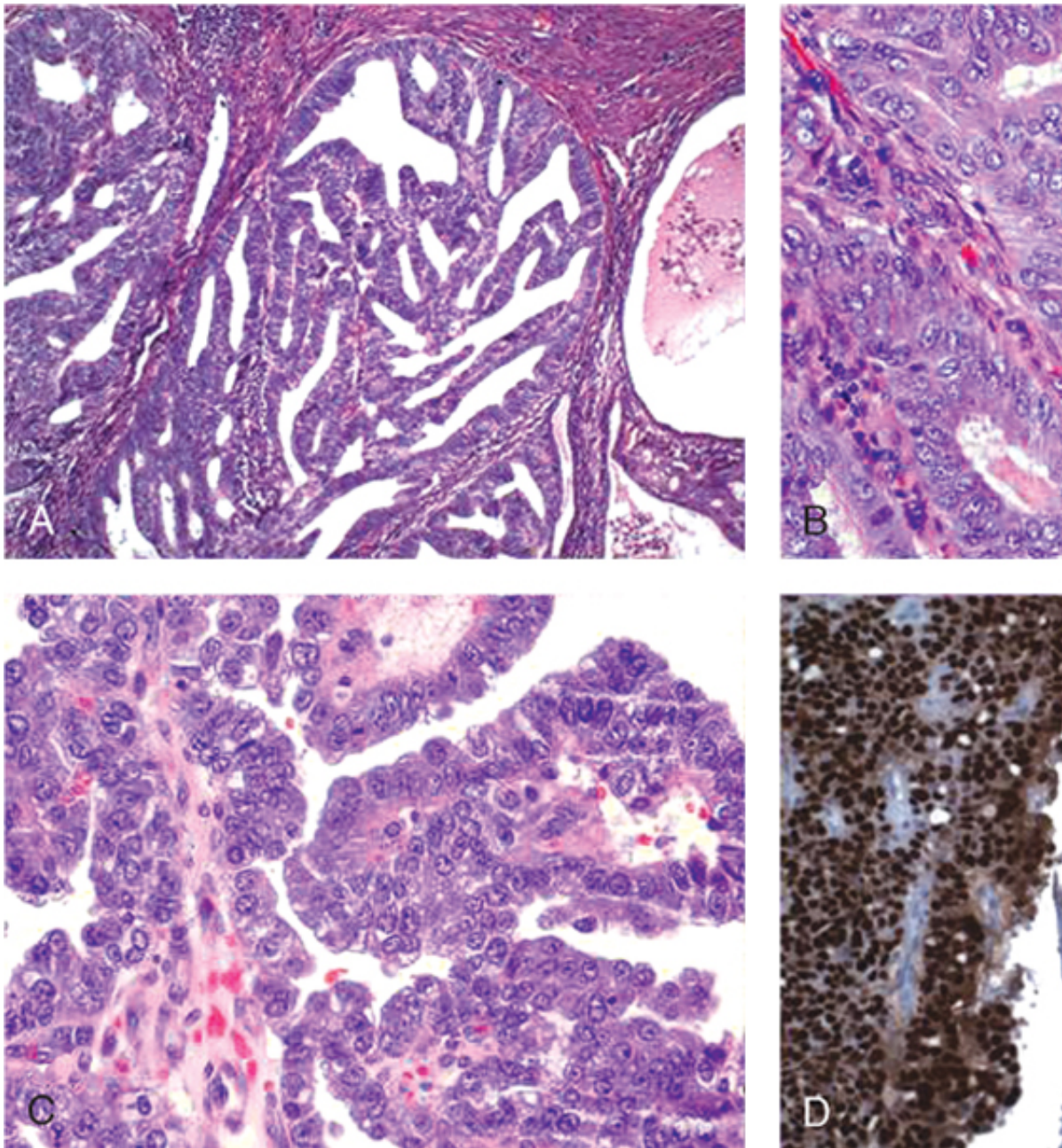
Serous carcinoma of the endometrium is pathophysiologically distinct. It typically arises in a background setting of an endometrial polyp. Mutations in DNA mismatch repair genes and *PTEN* are rare in serous carcinoma. Serous carcinoma cases have mutations in the *p53* tumor suppressor gene.

### **Morphology**

**Endometrioid carcinomas** closely resemble normal endometrium and may be examined by light microscopy (Fig. 19-14A, B). They frequently show a range of patterns, including mucinous, tubal (occasionally adenosquamous) differentiation. Tumors originate in the mucosa and myometrium and enter vascular spaces, with metastases to regional lymph nodes. Grading (grades I-III) and staging closely parallel outcome: stage I, confined to the uterus; stage II, involvement of the cervix; stage III, beyond the uterus but within the true pelvis; stage IV, involvement of other viscera. One exception is synchronous endometrioid tumor of the ovary. This scenario often signifies two separate primary neoplasms rather than stage migration, and has a less favorable prognosis. **Serous carcinoma** forms small tufts and papillae rather than endometrioid carcinoma, and has much greater cytologic atypia. They behave as high-grade cancers and are not graded, and are particularly aggressive (Fig. 19-14C, D).

cancers are not graded, and are particularly aggressive (Fig. 19-15, 19-16).

### Clinical Course



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 Figure 19-14 Endometrial carcinoma: **A**, Endometrioid type, infiltrating myometrium and displaying cribriform architecture, nuclear atypia, and loss of polarity. **C**, Serous carcinoma of the endometrium displaying formation of papillae and marked nuclear atypia. **D**, *p53* immunohistochemical staining reveals accumulation of mutant *p53* in serous carcinoma.

The first clinical indication of all endometrial carcinomas is marked leukorrhea and irregular bleeding in a postmenopausal woman, since it reflects erosion and ulceration of the endometrial surface. With time, the uterus becomes enlarged, and in time it becomes fixed to surrounding structures by extension of the cancer beyond the uterus. Although endometrial carcinoma is usually a late-metastasizing neoplasm, but dissemination eventually occurs, with involvement of regional lymph nodes. Stage I carcinoma is associated with a 5-year survival rate of 90%; this rate drops to 30% for stage IV disease.

in stages III and IV. The prognosis for papillary serous carcinomas is strongly dependent on the operative staging with peritoneal cytology. This is critical, since very small or superficial serous tumors of the fallopian tube to the peritoneal cavity.

## **SUMMARY**

### **Endometrial Carcinoma**

Clinically and molecularly there are two major types of endometrial carcinoma. *Endometrioid carcinoma* is associated with estrogen excess and endometrial hyperplasia. Molecular changes include inactivation of DNA mismatch repair genes and the *PTEN* gene. *Serous carcinoma* of the endometrium arises in older women, usually associated with endometrial atrophy. Molecular changes in the *p53* gene are an early event. Stage is the major determinant of survival. Serous carcinomas are more frequently with extrauterine extension and are therefore frequently of high grade.



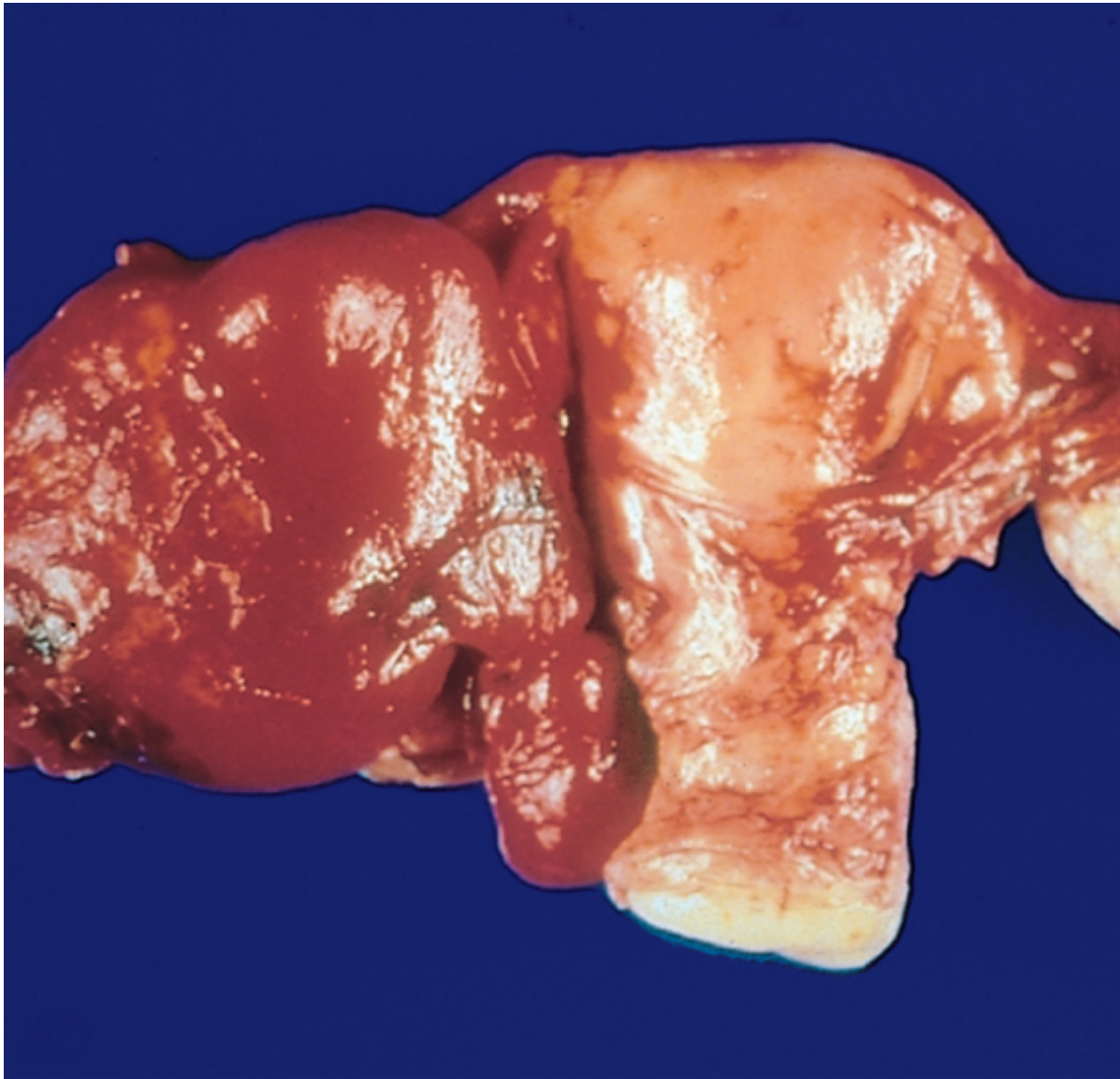
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## FALLOPIAN TUBES

The most common disease of the fallopian tubes is inflammation (salpingitis), almost always as a disease. Less common are ectopic (tubal) pregnancy, followed in order of frequency by endometriosis. A few comments on salpingitis and tumors follow.



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Figure 19-15 Pelvic inflammatory disease, asymmetric albeit bilateral. The left side has a large inflammatory mass less involved, but the tube is widely adherent to the still recognizable o

*Inflammations of the tube* are almost always microbial in origin. With the declining incidence of gonorrhea as *Chlamydia*, *Mycoplasma hominis*, coliforms, and (in the postpartum setting) streptococci and staphylococci as offenders. The morphologic changes produced by gonococci conform to those already described



differ in that they are more invasive, penetrating the wall of the tubes and thus tend more often to seeding of the meninges, joint spaces, and sometimes the heart valves. Tuberculous salpingitis is almost always in combination with tuberculosis of the endometrium. All forms of salpingitis may produce pain, and pelvic masses when the tubes become distended with either exudate or, later, burned-out debris (Fig. 19-15). Adherence of the tube to the ovary and adjacent ligamentous tissues results in a tubo-ovarian complex. Even more serious is the potential for adhesions of the tubal peritoneum, increasing the risk of tubal ectopic pregnancy (discussed below). Damage or obstruction of the tubal lumen results in sterility.

*Primary adenocarcinomas* of the fallopian tubes may be of papillary serous or endometrioid histology. In women with *BRCA* mutations, fallopian tube carcinomas seem to be increased. In studies of such women, 10% had occult foci of malignancy, equally divided between the ovary and fallopian fimbria. Because the lumen and fimbria of the fallopian tube have access to the peritoneal cavity, they often involve the omentum and peritoneal cavity at presentation.

## SUMMARY

### Fallopian Tube Disease

Salpingitis may be acute and clinically evident, as with gonorrhea, or chronic, caused by *Mycoplasma* or *Chlamydia*. Salpingitis results in scarring of the fallopian tube and may lead to tubal ectopic pregnancy. Extension beyond the fallopian tube gives rise to peritonitis. Fallopian tube carcinomas usually present at an advanced stage, with peritoneal cavity involvement.





## OVARIES

The ovaries are affected by physiologic changes involving the menstrual cycle, changes associated with aging, as well as a variety of tumors from its component tissues. In the U.S., carcinomas of the ovaries account for more deaths than do cancers of the cervix and uterine corpus together. It is less the frequency of the carcinomas than their lethality (because of their silent growth) that makes them so dangerous. Ovarian cysts are commonplace and can be broadly divided into those arising from the ovarian follicle and those with an epithelial lining.





## FOLLICLE AND LUTEAL CYSTS

Follicle and luteal cysts in the ovaries are so commonplace as almost to constitute physiologic variants. These innocuous lesions originate in unruptured graafian follicles or in follicles that have ruptured and immediately sealed. Such cysts are often multiple and develop immediately subjacent to the serosal covering of the ovary. Usually, they are small (1-1.5 cm in diameter) and are filled with clear serous fluid. Occasionally, they achieve diameters of 4 to 5 cm and may thus become palpable masses and produce pelvic pain. When small they are lined by granulosa lining cells or luteal cells, but as the fluid accumulates, pressure may cause atrophy of these cells. Sometimes these cysts rupture, producing intraperitoneal bleeding and acute abdominal symptoms.





## POLYCYSTIC OVARIES

Oligomenorrhea, hirsutism, infertility, and sometimes obesity may appear in young women (usually in girls after menarche) secondary to excessive production of estrogens and androgens (mostly the latter) by multiple cystic follicles in the ovaries. This condition is called *polycystic ovaries*, or *Stein-Leventhal syndrome*.

The ovaries are usually twice normal in size, are gray-white with a smooth outer cortex, and are studded with subcortical cysts 0.5 to 1.5 cm in diameter. Histologically, there is a thickened, fibrotic outer tunica, overlying innumerable cysts lined by granulosa cells with a hypertrophic and hyperplastic luteinized theca interna. There is a conspicuous absence of corpora lutea.

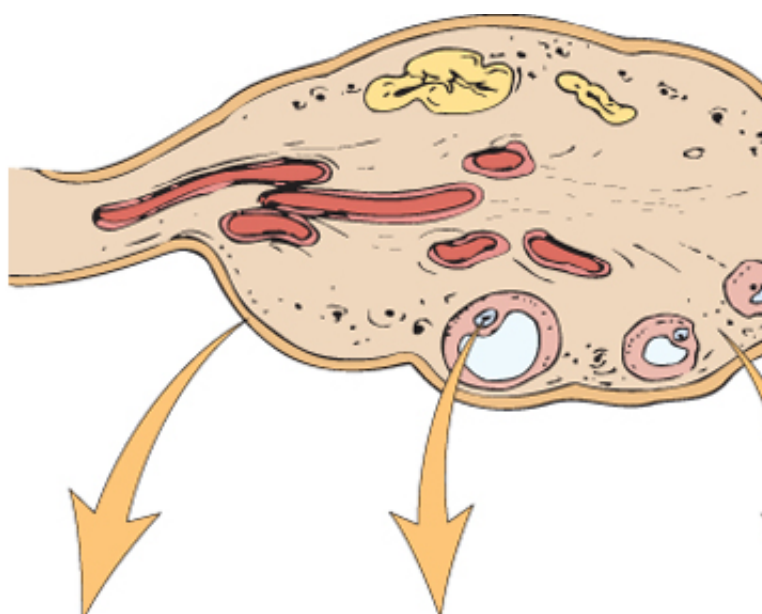
The principal biochemical abnormalities in most patients are excessive production of androgens, high concentrations of luteinizing hormone, and low concentrations of follicle-stimulating hormone. The origins of these changes are poorly understood, but it is proposed that the ovaries in this condition elaborate excess androgens, which are converted in peripheral fatty depots to [estrone<sup>R</sup>](#), and these, through the hypothalamus, inhibit the secretion of follicle-stimulating hormone by the pituitary. The basis of excess ovarian androgen secretion is mysterious.





## TUMORS OF THE OVARY

With more than 23,000 new cases diagnosed annually, ovarian cancer is the fifth most common cancer and a leading cause of cancer death in women, with close to 14,000 deaths estimated in 2006. Tumors are diverse pathologic entities. This diversity is attributable to the three cell types that make up the normal ovary: surface covering epithelium, the totipotential germ cells, and the multipotential sex cord/stromal cells. Each type gives rise to a variety of tumors (Fig. 19-16).



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD/STROMAL CELL
Overall frequency	65%–70%	15%–20%	5%
Proportion of malignant ovarian tumors	90%	3%–5%	2%
Age group affected	20+ years	0–25+ years	1–50 years
Types	<ul style="list-style-type: none"> <li>• Serous tumor</li> <li>• Mucinous tumor</li> <li>• Endometrioid tumor</li> <li>• Clear cell tumor</li> <li>• Brenner tumor</li> <li>• Cystadenofibroma</li> </ul>	<ul style="list-style-type: none"> <li>• Teratoma</li> <li>• Dysgerminoma</li> <li>• Endodermal sinus tumor</li> <li>• Choriocarcinoma</li> </ul>	<ul style="list-style-type: none"> <li>• Fibroma</li> <li>• Granulosa cell tumor</li> <li>• Sertoli cell tumor</li> </ul>

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Figure 19-16 Derivation of various ovarian neoplasms and some data on their frequency.

Neoplasms of surface epithelial origin account for the great majority of primary ovarian tumors, an almost 90% of ovarian cancers. Germ-cell and sex cord/stromal cell tumors are much less frequent.

almost 50% of ovarian cancers. Germ cell and sex cord-stromal cell tumors are much less frequent. 30% of ovarian tumors, are collectively responsible for fewer than 10% of malignant tumors of the

### *Pathogenesis*

Several risk factors for epithelial ovarian cancers have been recognized. Two of the most important is a higher incidence of carcinoma in unmarried women and married women with low parity. Intercourse with oral contraceptives reduces the risk somewhat. Although only 5% to 10% of ovarian cancers are familial, the molecular pathogenesis of these cancers by identifying the culprit genes in these cases. A majority of familial cases can be caused by mutations in the *BRCA* genes, *BRCA1* and *BRCA2*. These, as will be discussed later, are also associated with breast cancer. Indeed, with mutations in these genes there is increased risk for both ovarian and breast cancer. For ovarian cancer approximates 30% in *BRCA1* carriers, with figures varying from 16% to 44% in carriers is somewhat lower. Although mutations in *BRCA* genes are present in the majority of the familial cases, mutations are seen in only 8% to 10% of sporadic ovarian cancers. Thus, there must be other molecular factors involved. For example, the protein HER2/NEU is overexpressed in 35% of ovarian cancers, and is associated with a poor prognosis. It is overexpressed in up to 30% of tumors, mostly mucinous cystadenocarcinomas. As with other cancers, the pathogenesis of ovarian cancers.



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## SURFACE EPITHELIAL-STROMAL TUMORS

These neoplasms are derived from the coelomic mesothelium that covers the surface of the ovary; the surface epithelium is pulled into the cortex of the ovary, forming small epithelial cysts. These cysts may undergo transformation into epithelial tumors of the various histologic types. Benign lesions are usually cystic, often with an accompanying stromal component (cystadenofibroma). Malignant tumors may also be cystic (cystadenocarcinoma). The surface epithelial tumors also have an intermediate, borderline category currently referred to as atypical serous tumors. These seem to be low-grade cancers with limited invasive potential. Thus, they have a better prognosis than most carcinomas.

### Serous Tumors

These are the most frequent of the ovarian tumors. Benign lesions are usually encountered between 45 and 65 years of age. About 60% are benign and 40% are malignant. Combined, borderline and malignant serous tumors are the most common malignant ovarian tumors.

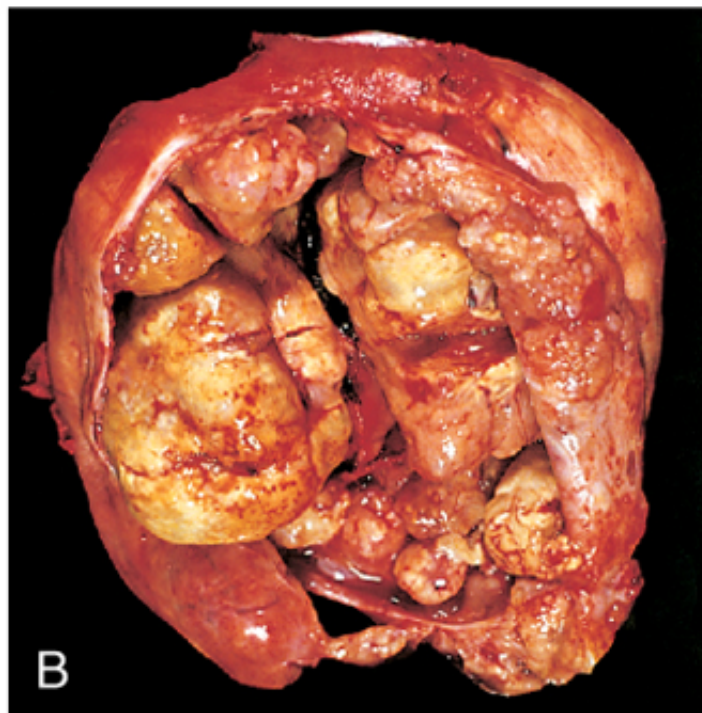
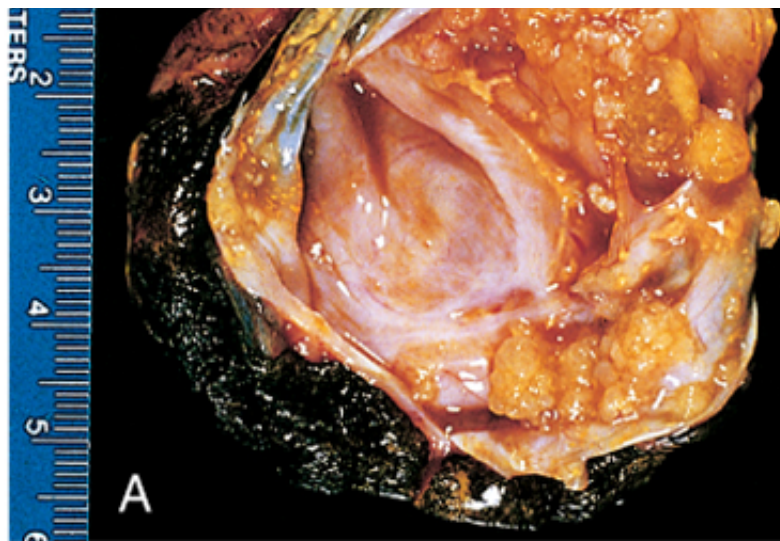
#### Morphology

Grossly, serous tumors may be small (5-10 cm) in diameter, but most are large, solid, and complex structures, as large as 30 to 40 cm in diameter. **About 25% of the benign forms are cystic.** In this form, the serosal covering is smooth and glistening. In contrast, the surface of the solid tumor shows nodular irregularities, which represent penetration of the tumor to or through the capsule. On transection, the small cystic tumor may reveal a single cavity, but larger ones are divided by septa into a multiloculated mass (Fig. 19-17). The cystic spaces are usually filled with clear fluid, although a considerable amount of mucus may also be present. Jutting into the cystic spaces are papillary projections, which become more marked in malignant tumors (see Fig. 19-18).

Histologically, the benign tumors are characterized by a single layer of **tall columnar** cells lining the cyst or cysts. The cells are in part ciliated and in part dome-shaped secretory cells. Concentrically laminated calcified concretions (psammoma bodies) are common in the tips of papillae. In malignant forms, anaplasia of the lining cells appears, as does invasion of the stroma. Papillary tumors are complex and multilayered, with invasion of the axial fibrous tissue by nests or trabeculae of malignant cells. Between these clearly benign and obviously malignant forms are the **malignant potential** tumors, with milder cytologic atypia and typically, little or no stromal invasion. These malignant potential tumors may seed the peritoneum, but typically the implants of tumor are small. Occasionally, tumors of low malignant potential may present with "invasive" peritoneal implants as carcinoma. Retrospective histologic studies of these tumors often reveal a great deal of complexity and cellular anaplasia. A micropapillary variant of serous low malignant potential tumor has been described that seems to have a worse prognosis and seems to evolve from a conventional malignant potential tumor. Mutations in *BRAF* and *K-RAS* are common in tumors of low malignant potential, by contrast, have mutations in *p53* and *BRCA1*, and typically lack mutations in *RAS* and *BRAF*.

In general, malignant serous tumors spread to regional lymph nodes, including peritoneal and distant lymphatic and hematogenous metastases are infrequent.





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Figure 19-17 **A**, Borderline serous cystadenoma opened to display a cyst cavity lined by delicate papillary tumor  
opened to reveal a large, bulky tumor mass. (Courtesy of Dr. Christopher Crum, Brigham and Women

The prognosis for the individual with clearly invasive serous cystadenocarcinoma after surgery, radiation, and chemotherapy depends heavily on the stage of the disease at the time of diagnosis. If the tumor appears to be clearly invasive, the prognosis for carcinomatous lesions yield a 5-year survival of about 70%, whereas tumors of low malignant potential yield a 5-year survival of nearly 100%. With cancers that have penetrated the capsule, the 10-year survival rate is only 13%. The 5-year survival rate for low malignant potential tumors is nearly 100%, and even with peritoneal metastases it is nearly 75%, although almost all of their tumors.

### Mucinous Tumors

Mucinous tumors are in most respects analogous to the serous tumors, differing essentially in the secretory cells similar to those of the endocervical mucosa. These tumors occur in women in the same age group as the serous tumors, but mucinous lesions are considerably less likely to be malignant, accounting for about 10% of all ovarian tumors.



mucinous tumors are malignant (*cystadenocarcinomas*), while 10% are of low malignant potential

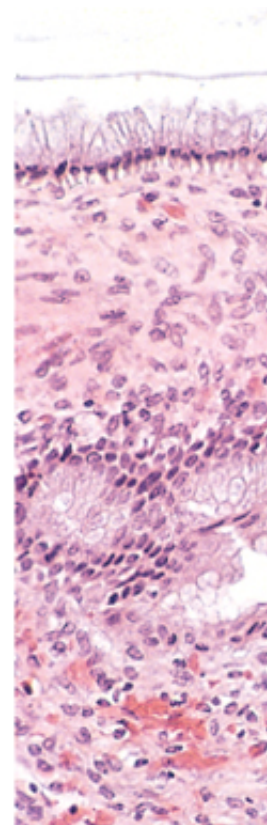
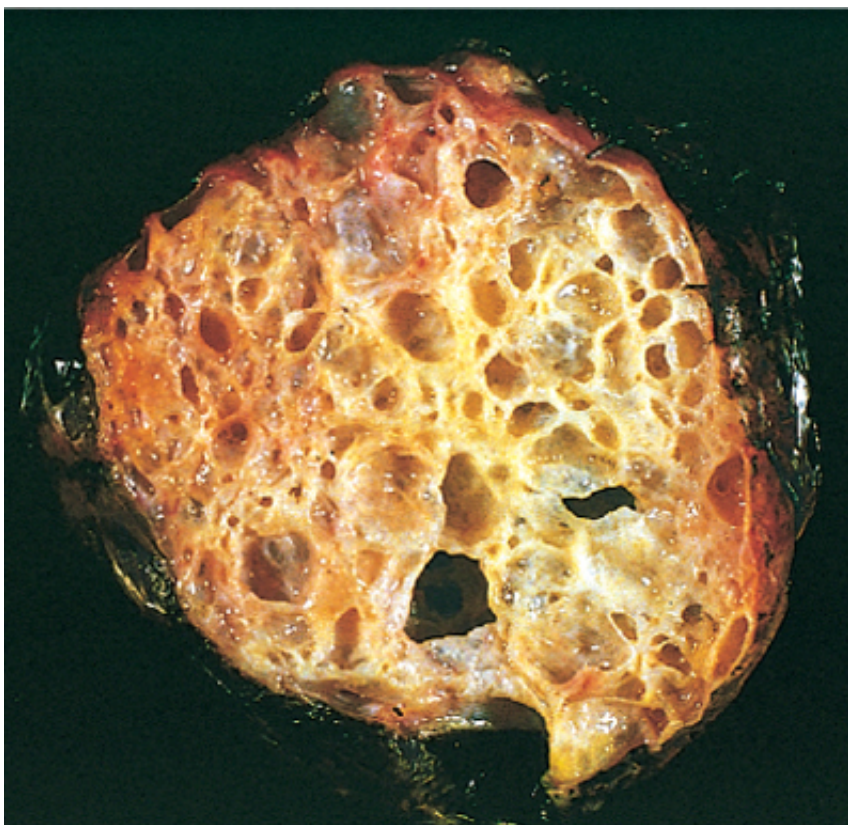
### Morphology

Only about 5% of benign and 20% of malignant mucinous tumors are bilateral, a m for their serous counterparts. Bilateral mucinous tumors of the ovary must be differ adenocarcinomas of the gastrointestinal tract, which may present as ovarian mass

On gross examination they may be indistinguishable from serous tumors except by the cystic contents. However, **they are more likely to be larger and multilocular formations are less common (Fig. 19-18A).** (Unlike in their serous counterpart are not found within the tips of the papillae.) **Prominent papillation, serosal p areas point to malignancy.**

Histologically, mucinous tumors are classified according to the character of the mu cells. Essentially three types may be identified. The first two, which are not always tumors with endocervical and intestinal-type epithelia (Fig. 19-18B). The latter is al mucinous tumors with low malignant potential, and mucinous carcinomas. The thir mucinous cystadenoma, which is typically associated with an endometriotic cyst. T represents an endometrial tumor with mucinous differentiation.

Rupture of mucinous tumors may result in mucinous deposits in the peritoneum; he not result in long-term growth of tumor in the peritoneum. Implantation of mucinous peritoneum with production of copious amounts of mucin is called **pseudomyxoma**; majority if not all cases of pseudomyxoma peritonei are caused by metastasis from primarily the appendix (Chapter 15). Metastasis of mucinous tumor of the gastroint (the so-called **Krukenberg tumor**) may also mimic an ovarian primary tumor. Clue gastrointestinal tumor include bilateral ovarian involvement, infiltration of the strom individual cells, and "dirty" necrosis of the tumor (necrosis associated with cellular





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 Figure 19-18 **A**, A mucinous cystadenoma with its multicystic appearance and delicate septa. Note the presence of the cell lining of mucinous cystadenoma.

The prognosis of mucinous cystadenocarcinoma is somewhat better than that for the serous counterpart. The histologic type is the major determinant of treatment success.

### Endometrioid Tumors

These tumors may be solid or cystic, but sometimes they develop as a mass projecting from the surface of the ovary and filled with chocolate-colored fluid. Microscopically they are distinguished by the formation of tubular glands, within the linings of cystic spaces. Although benign and borderline forms exist, endometrioid tumors are bilateral in about 30% of cases, and 15% to 30% of women with these ovarian tumors have a concurrent endometrial cancer, endometrioid carcinomas have mutations in the *PTEN* suppressor gene.

### Brenner Tumor

The Brenner tumor is an uncommon, solid, usually unilateral ovarian tumor consisting of an abundance of transitional-like epithelium resembling that of the urinary tract. Occasionally, the nests are cystic and contain secretory cells. Brenner tumors are generally smoothly encapsulated and gray-white on transection. They are usually 1 to 2 cm in diameter. These tumors may arise from the surface epithelium or from urogenital epithelium. Rarely, they are formed as nodules within the wall of a mucinous cystadenoma. Although most are benign, some have been described as malignant.



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## OTHER OVARIAN TUMORS

Many other types of tumors of germ-cell or sex cord/stromal origin also arise in the ovary, but only sufficiently common to be described here. [Table 19-2](#) presents some salient features of a few other origin. Interestingly, the testis, essentially an identical gonad in the early embryo until sex determination of tumor formation. Epithelial tumors are vanishingly rare in the testis, benign cystic teratomas are tumors are the most common.

### Teratomas

**Table 19-2. Selected Ovarian Neoplasms**

	Peak Incidence	Usual Location	Morphologic Features
<b>Germ-Cell Origin</b>			
Dysgerminoma	Second to third decades Occur with gonadal dysgenesis	80% to 90% unilateral	Counterpart of testicular seminoma. Solid large to small gray masses. Sheets or cords of large cleared cells separated by scant fibrous strands. Stroma may contain lymphocytes and occasional granuloma.
Choriocarcinoma	First three decades of life	Unilateral	Identical to placental tumor. Often small, hemorrhagic focus with two types of epithelium; cytotrophoblast and syncytiotrophoblast.
<b>Sex Cord Tumors</b>			
Granulosa-thecal cell	Most postmenopausal but at any age	Unilateral	May be tiny or large, gray to yellow (with cystic spaces). Composed of mixture of cuboidal granulosa cells in cords, sheets, or strands and spindled or plump lipid-laden thecal cells. Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies.
Thecoma-fibroma	Any age	Unilateral	Solid gray fibrous cells to yellow (lipid-laden) plump thecal cells.
Sertoli-Leydig cell	All ages	Unilateral	Usually small, gray to yellow-brown, and solid. Recaps development of testis with tubules, or cords and plump pink Sertoli cells.
<b>Metastases to Ovary</b>			
	Older ages	Mostly bilateral	Usually solid gray-white masses as large as 20cm in diameter. Anaplastic tumor cells, cords, glands, dispersed through fibrous background. Cells may be "signet-ring" mucin-secreting.

These neoplasms of germ-cell origin constitute 15% to 20% of ovarian tumors. They display the two decades of life, and the younger the person, the greater is the likelihood of malignancy. However, neoplasms are benign mature cystic teratomas. The immature malignant variant is rare.

### **Benign (Mature) Cystic Teratomas**

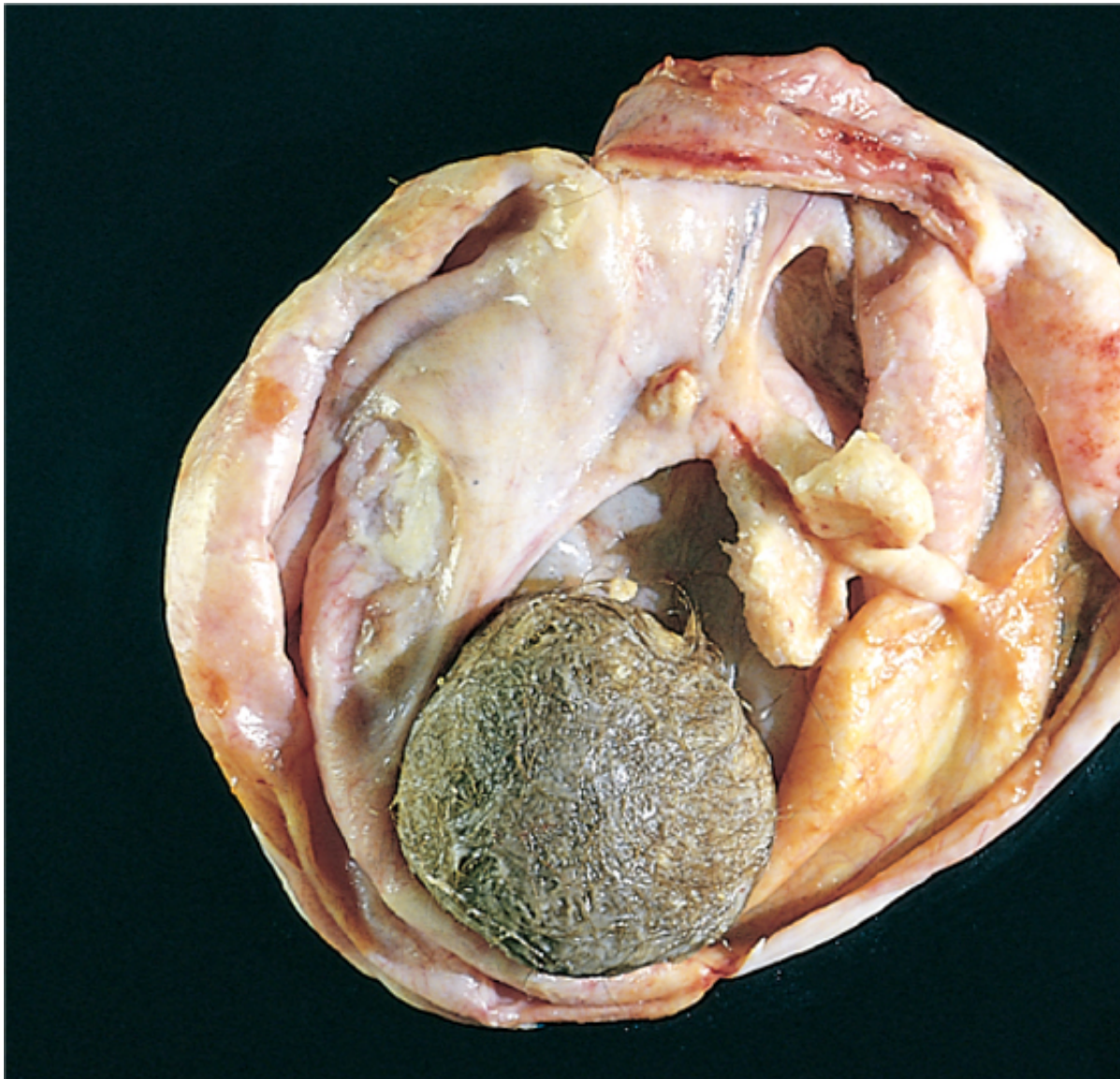
Almost all of these neoplasms are marked by differentiation of totipotential germ cells into mature layers: ectoderm, endoderm, and mesoderm. Usually there is the formation of a cyst lined by recc appendages hence the common designation dermoid cysts. Most are discovered in young women



appendages-hence the common designation *dermoid cysts*. Most are discovered in young women incidentally on abdominal radiographs or scans because they contain foci of calcification produced unilaterally, more often on the right. Rarely do these cystic masses exceed 10 cm in diameter. On transverse section, they reveal a hair-bearing epidermal lining (keratinous projection) from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial carcinoma, or recognizable lines of development are also present.

For unknown reasons these neoplasms sometimes produce infertility. In about 1% of cases there are malignant tissue elements, usually taking the form of a squamous cell carcinoma. Also, for unknown reasons, ovarian torsion (10% to 15% of cases), producing an acute surgical emergency.

### ***Immature Malignant Teratomas***



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Figure 19-19 Opened mature cystic teratoma (dermoid cyst) of the ovary. A ball of hair (*bottom*) and a mixture of other tissues (top) are visible. (Courtesy of Dr. J. H. Crum, Brigham and Women's Hospital, Boston, Massachusetts.)

These neoplasms are found early in life, the mean age being 18 years. They differ strikingly from other ovarian neoplasms in that they are often bulky, are predominantly solid or near-solid on transection, and are punctuated here and there by cystic foci. One of the cystic foci may contain sebaceous secretion, hair, and other features similar to those in



the distinguishing feature is a variety of immature or barely recognizable areas of differentiation to other structures. Particularly ominous are foci of neuroepithelial differentiation, because most such are widely. Immature teratomas are both graded and staged in an effort to predict their future. Those with appropriate therapy, whereas the opposite end of the spectrum carries a much graver outlook.

### **Specialized Teratomas**

These curiosities are mentioned only because they tend to evoke "I don't believe it" reactions. Struma ovarii is thyroid tissue that, interestingly, may hyperfunction and produce hyperthyroidism. These tumors are also ovarian masses. Equally incongruous is the ovarian carcinoid, which in rare instances has produced medicine long enough, you may come across a combined struma ovarii and carcinoid in the same ovary. Elements may become malignant.

### **Clinical Correlations for All Ovarian Tumors**

All ovarian neoplasms pose formidable clinical challenges, because they produce no symptoms or signs. The clinical presentation of all ovarian tumors is remarkably similar despite their great morphologic diversity. Ovarian tumors of surface cell origin are usually asymptomatic but may cause local pressure symptoms (e.g., pain, gastrointestinal complaints, urinary frequency). Indeed, many are discovered incidentally on routine gynecologic examination. Larger masses, notably the common serous cystadenomas, are found in abdominal girth. Smaller masses, particularly dermoid cysts, sometimes become twisted on the ovarian pedicle, causing abdominal pain mimicking an "acute abdomen." Fibromas and malignant serous tumors often cause metastatic seeding of the peritoneal cavity, so that tumor cells can be identified in the ascitic fluid. Attention is also drawn to attention because of the endocrinopathies they induce.

Unfortunately, treatment of ovarian tumors remains unsatisfactory, as proved by the only modest improvement achieved since the mid-1970s. Screening detection methods are being developed, but to this point no reliable method for the early detection of ovarian cancers while they are still curable. Among the many markers that have been explored, elevated levels of CA-125 have been reported in 75% to 90% of women with epithelial ovarian cancer. However, this protein is not specific for cancer, with cancer limited to the ovary and, moreover, it is present in high concentrations in a variety of other cancers. It is useful as a screening test in asymptomatic postmenopausal women because of the high sensitivity. However, as with carcinoembryonic antigen in colon cancer ([Chapter 15](#)), CA-125 measurements are of limited value in response to therapy.

### **SUMMARY Ovarian Tumors**

Tumors may arise from any of the major components of the ovary: surface epithelium, stroma, and follicle lining granulosa cells, or germ cells. Epithelial tumors are the most common ovarian tumors and are more common in women older than 40 years of age. Epithelial tumors are serous, endometrioid, and mucinous. Each has a benign or malignant potential (borderline) counterpart. Germ-cell tumors (mostly cystic) are the second most common ovarian tumor in young women; the majority are benign. Germ-cell tumors may differentiate toward oögonia (dysgerminoma), primitive embryonal tissue (embryonal), yolk-sac tumor (endodermal sinus tumor), placental tissue (choriocarcinoma), or multiple fetal tissues (teratoma). Depending on differentiation, they may produce estrogens or androgens.





## DISEASES OF PREGNANCY

Diseases of pregnancy and pathologic conditions of the placenta are important causes of intrauterine or perinatal death, premature birth, congenital malformations, intrauterine growth retardation, maternal death, and a great deal of morbidity for both mother and child. Here we discuss only a limited number of disorders in which knowledge of the morphologic lesions contributes to an understanding of the clinical problem.





## PLACENTAL INFLAMMATIONS AND INFECTIONS

Infections reach the placenta by two pathways: (1) ascending infection through the birth canal and (2) hematogenous (transplacental) infection.

*Ascending infections* are by far the most common; in most instances, they are bacterial and are associated with premature birth and premature rupture of the membranes. The chorioamnion shows polymorphonuclear leukocytic infiltration with edema and congestion of the vessels (acute chorioamnionitis). When the infection extends beyond the membranes, it may involve the umbilical cord and placental villi and cause acute vasculitis of the cord. Ascending infections are caused by mycoplasmas, *Candida*, and the numerous bacteria of the vaginal flora. Uncommonly, placental infections may arise by the *hematogenous spread* of bacteria and other organisms; histologically, the villi are most often affected (villitis). Syphilis, tuberculosis, listeriosis, toxoplasmosis, and various viruses (rubella, cytomegalovirus, herpes simplex) can all cause placental villitis. Transplacental infections can affect the fetus and give rise to the so-called TORCH complex ([Chapter 7](#)).





## ECTOPIC PREGNANCY

Ectopic pregnancy is implantation of the fertilized ovum in any site other than the normal uterine location. The condition occurs in as many as 1% of pregnancies. In more than 90% of these cases, implantation is in the oviducts (tubal pregnancy); other sites include the ovaries, the abdominal cavity, and the intrauterine portion of the oviducts (interstitial pregnancy). Any factor that retards passage of the ovum along its course through the oviducts to the uterus predisposes to an ectopic pregnancy. In about half of the cases, such obstruction is based on chronic inflammatory changes in the oviduct, although intrauterine tumors and endometriosis may also hamper passage of the ovum. In approximately 50% of tubal pregnancies, no anatomic cause can be demonstrated. Ovarian pregnancies probably result from those rare instances where the ovum is fertilized within its follicle just at the time of rupture. Gestation within the abdominal cavity occurs when the fertilized egg drops out of the fimbriated end of the oviduct and implants on the peritoneum.

### Morphology

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In all sites, ectopic pregnancies are characterized by fairly normal early development of the embryo, with the formation of placental tissue, the amniotic sac, and decidual changes. An abdominal pregnancy is occasionally carried to term. With tubal pregnancies, however, the invading placenta eventually burrows through the wall of the oviduct, causing **intratubal hematoma (hematosalpinx)**, **intraperitoneal hemorrhage**, or both. The tube is usually locally distended as much as 3 to 4 cm by a contained mass of freshly clotted blood in which may be seen bits of gray placental tissue and fetal parts. The histologic diagnosis depends on the visualization of placental villi or, rarely, of the embryo. Less commonly, poor attachment of the placenta to the tubal wall results in death of the embryo, with spontaneous proteolysis and absorption of the products of conception.

Until rupture occurs, an ectopic pregnancy may be indistinguishable from a normal one, with cessation of menstruation and elevation of serum and urinary placental hormones. Under the influence of these hormones, the endometrium (in ~50% of cases) undergoes the characteristic hypersecretory and decidual changes. However, the absence of elevated gonadotropin levels does not exclude this diagnosis, because poor attachment with necrosis of the placenta is common. Rupture of an ectopic pregnancy may be catastrophic, with the sudden onset of intense abdominal pain and signs of an acute abdomen, often followed by shock. Prompt surgical intervention is necessary.

### SUMMARY

#### Ectopic Pregnancy

Any implantation outside the uterine corpus is ectopic; the most common site is a fallopian tube. Chronic salpingitis with scarring is a major risk factor for tubal ectopic pregnancy. Approximately 1% of pregnancies implant ectopically. Rupture of an ectopic pregnancy is a medical emergency that may result in exsanguination and death.





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## GESTATIONAL TROPHOBLASTIC DISEASE

Traditionally, the gestational trophoblastic tumors have been divided into three overlapping morphologic types: *invasive mole*, and *choriocarcinoma*. They range in level of aggressiveness from the hydatidiform mole to the highly malignant choriocarcinomas. All elaborate human chorionic gonadotropin (hCG), which can be found in urine at titers considerably higher than those found during normal pregnancy; the titers progressively increase from the hydatidiform mole to choriocarcinoma. In addition to aiding diagnosis, the fall or (alternatively) rise in the level of hCG in urine can be used to monitor the effectiveness of treatment. Clinicians therefore prefer the term *gestational trophoblastic disease* to encompass the response to therapy as judged by the hormone titers is significantly more important than any specific histologic lesion from another. Nonetheless, it is necessary to understand their individual characteristics to

### Hydatidiform Mole: Complete and Partial

The typical hydatidiform mole is a voluminous mass of swollen, sometimes cystically dilated, chorionic villi. The swollen villi are covered by varying amounts of normal to highly atypical chorionic epithelium. Moles have been characterized: *complete* and *partial* moles. The complete hydatidiform mole does not contain fetal parts. All of the chorionic villi are abnormal, and the chorionic epithelium is abnormal (commonly, 46,XX). The partial hydatidiform mole is compatible with early embryo formation and contains normal chorionic villi, and is almost always triploid (e.g., 69,XXY; Table 19-3). The two patterns result from either a complete mole an empty egg is fertilized by two spermatozoa (or a diploid sperm), yielding a diploid karyotype with two paternal genes, while in a partial mole a normal egg is fertilized by two spermatozoa (or a diploid sperm), yielding a triploid karyotype with a preponderance of paternal genes.

The incidence of complete hydatidiform moles is about 1 to 1.5 per 1000 pregnancies in the United States. For unknown reasons there is a much higher incidence in Asian countries. Moles are most common in the second trimester, and a history of the condition increases the risk in subsequent pregnancies. Although traditionally diagnosed late in pregnancy because of a gestation that was "too large for dates," early monitoring of pregnancies by ultrasound has led to an earlier age of detection, leading to the more frequent diagnosis of "early complete hydatidiform mole." Incomplete moles are diagnosed by ultrasound and absence of fetal parts or fetal heart sounds are typical.

Table 19-3. Features of Complete and Partial Hydatidiform Mole

Feature	Complete Mole	Partial Mole
Karyotype	46,XX (46,XY)	Triploid
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse; circumferential	Focal
Atypia	Often present	Absent
Serum hCG	Elevated	Less elevated
hCG in tissue	++++	+
Behavior	2% choriocarcinoma	Rare

hCG, human chorionic gonadotropin.

### Morphology

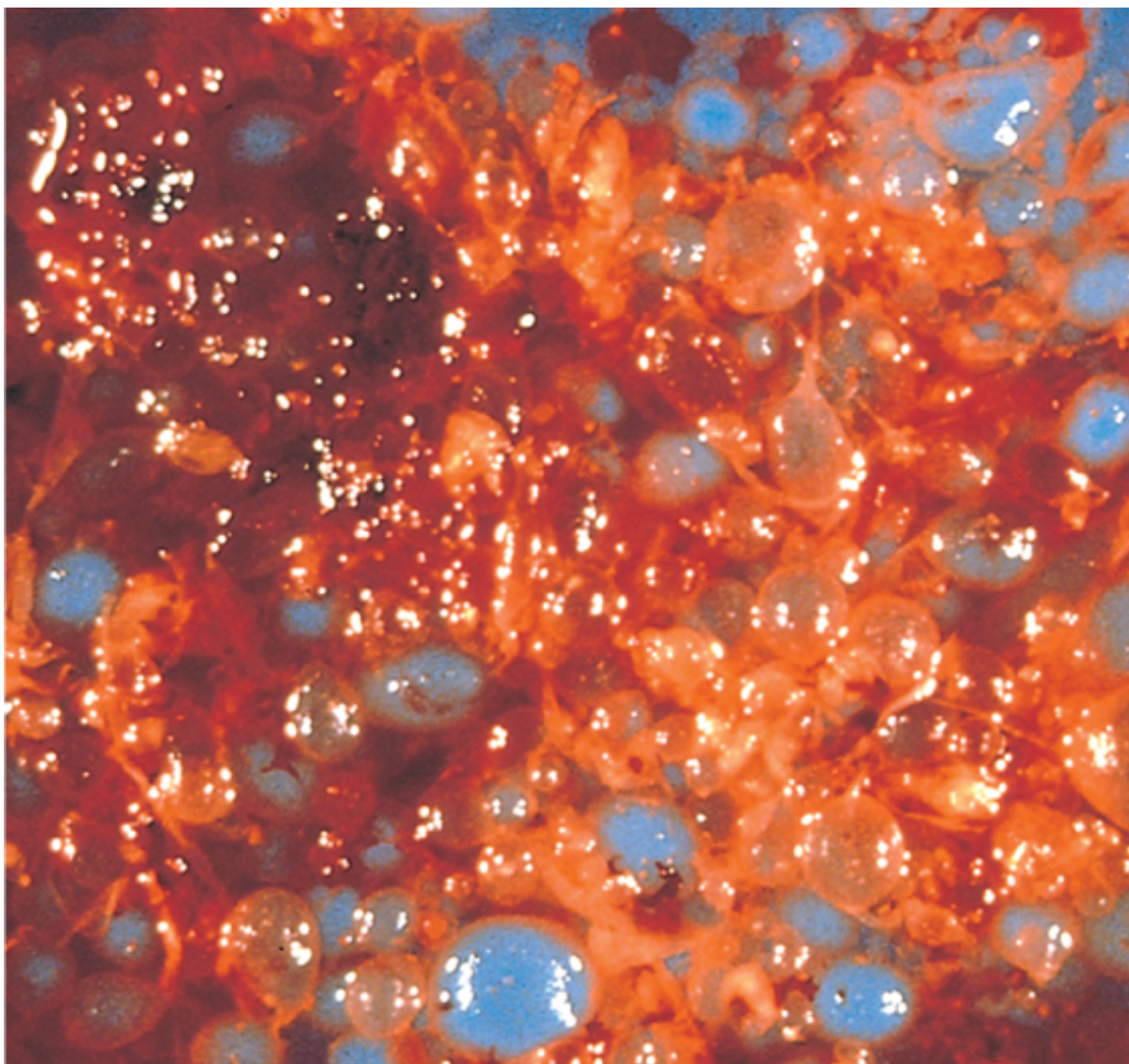
The uterus may be normal in size (as in early moles), but in fully developed cases it is enlarged and contains a delicate, friable mass of thin-walled, translucent cystic structures (Fig. 19-20). These cysts are seen in complete moles but are common in partial moles. Microscopically, the complete mole is characterized by the hydropic swelling of chorionic villi and virtual absence of vascularization of villi. The villi is a loose, myxomatous, edematous stroma. The chorionic epithelium almost always shows evidence of proliferation of both cytotrophoblast and syncytiotrophoblast (Fig. 19-21). The partial mole is characterized by the presence of normal chorionic villi but in many cases there is striking circumferential hyperplasia. Histologic grading of

outcome of moles has been supplanted by careful following of hCG levels. In **partial** edema involves only some of the villi and the trophoblastic proliferation is focal and moles have a characteristic irregular scalloped margin. In most cases of partial moles, an embryo or fetus. This may be in the form of fetal red blood cells in placental villi or, a malformed fetus that, despite a triploid karyotype, is morphologically nearly normal in appearance.

Overall, 80% to 90% of moles do not recur after thorough curettage; 10% of complete moles are known to give rise to choriocarcinoma. Partial moles rarely give rise to choriocarcinomas. With complete moles, urinary hCG concentrations, particularly the more definitive  $\beta$ -subunit of the hormone, permits detection of a serious complication and leads to the institution of appropriate therapy, including in some cases curative.

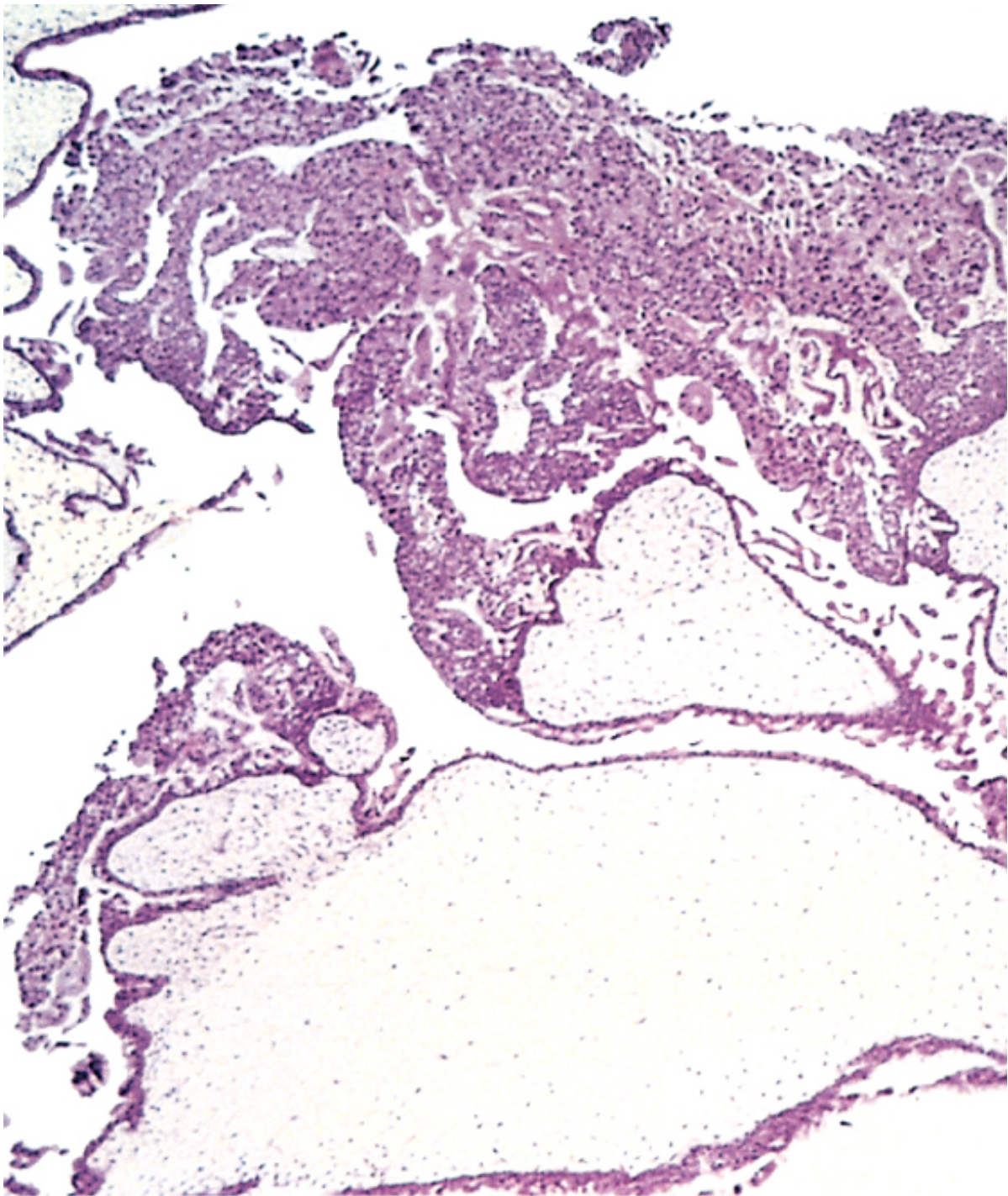
### **Invasive Mole**

Invasive moles are complete moles that are more invasive locally but do not have the aggressive



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Figure 19-20 Complete hydatidiform mole suspended in saline showing numerous swollen





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 Figure 19-21 A microscopic image of a complete mole showing distended hydropic villi (*below*) and proliferation of trophoblastic tissue.  
 Kyle Molberg, Department of Pathology, University of Texas Southwestern Medical School

An invasive mole retains hydropic villi, which penetrate the uterine wall deeply, possibly causing necrosis and hemorrhage. Local spread to the broad ligament and vagina may also occur. Microscopically, the villi show hyperplastic and atypical changes, with proliferation of both cuboidal and syncytial components.

Although the marked invasiveness of this lesion makes removal technically difficult, metastases do not occur. Although the marked invasiveness of this lesion makes removal technically difficult, metastases do not occur. Although the marked invasiveness of this lesion makes removal technically difficult, metastases do not occur. Although the marked invasiveness of this lesion makes removal technically difficult, metastases do not occur. Because of the greater depth of invasion into the myometrium, an invasive mole is difficult to remove.



therefore serum hCG may remain elevated. This alerts the clinician to the need for further treatment possible through chemotherapy.

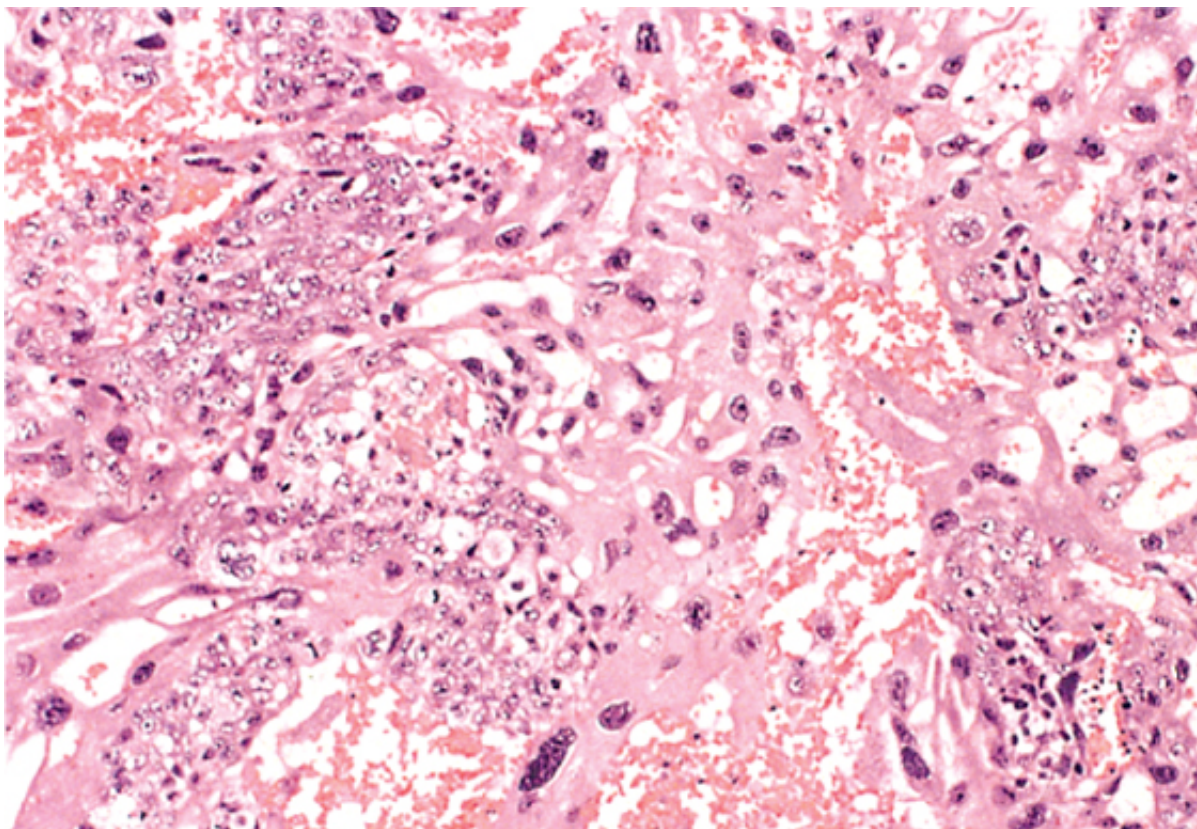
### Choriocarcinoma

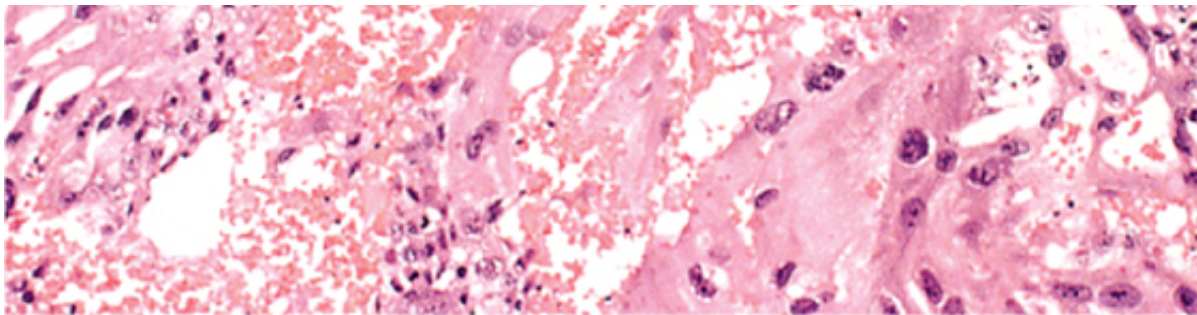
This very aggressive malignant tumor arises either from gestational chorionic epithelium or, less frequently, from the gonads or elsewhere. Choriocarcinomas are rare in the Western hemisphere, and in the United States, they are most common in pregnancies. They are much more common in Asian and African countries, reaching a frequency somewhat greater before age 20 and is significantly elevated after age 40. Approximately 50% of choriocarcinomas arise from hydatidiform moles; about 25% arise after an abortion, and most of the remainder occur during or after a normal pregnancy. In any case, the more abnormal the conception, the greater is the risk of developing gestational choriocarcinoma. The tumor is usually discovered by the appearance of a bloody, brownish discharge accompanied by a rising titer of hCG in the blood and urine, and the absence of marked uterine enlargement, such as would be anticipated with a normal pregnancy. In those instances that follow abortion or pregnancy, the maternal age and increasing frequency of this neoplasm suggests an origin from an abnormal ovum.

#### Morphology

Choriocarcinomas usually appear as very hemorrhagic, necrotic masses within the uterus. The necrosis is so complete that anatomic diagnosis is difficult. Indeed, the primary lesion is often obscured by the metastases. Very early, the tumor insinuates itself into the myometrium and into the blood vessels. **In contrast to the case with hydatidiform moles and invasive moles, the tumor is purely epithelial, composed of anaplastic cuboidal cells and syncytiotrophoblast (Fig. 19-22).**

By the time most choriocarcinomas are discovered, there is usually widespread dissemination via the blood (30% to 40%), brain, liver, and kidneys. Lymphatic invasion is uncommon.





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Figure 19-22 Photomicrograph of choriocarcinoma illustrating both neoplastic cytotrophoblast and syncytiotrophoblast (H&E, 100×, and Women's Hospital, Boston, Massachusetts.)

Despite the extreme aggressiveness of these neoplasms, which made them nearly uniformly fatal, treatment has achieved remarkable results. Nearly 100% of cases can be cured, even with neoplasms that have metastasized to the vagina and into the lungs. Equally remarkable are reports of healthy infants born later to these women despite a poor response to chemotherapy in choriocarcinomas that arise in the gonads (ovary or testis). This is related to the presence of paternal antigens on placental choriocarcinomas but not on gonadal lesions. The immune response against the foreign (paternal) antigens helps by acting as an adjunct to chemotherapy.

### Placental Site Trophoblastic Tumor

These uncommon tumors are diploid, are often XX in karyotype, and are derived from the placenta. They typically arise a few months after a pregnancy. Because intermediate trophoblasts do not produce hCG, hCG concentrations are elevated, but only slightly. More typically these tumors produce human placental lactogen (hPL) and generally have a favorable outcome if confined to the endomyometrium. However, they are not trophoblastic tumors, and the prognosis is poor when spread has occurred beyond the uterus.

## SUMMARY

### Gestational Trophoblastic Disease

Molar disease is due to an abnormal contribution of paternal chromosomes. Complete moles are triploid and have two sets of paternal chromosomes. They are typically derived from a triploid embryo or fetus. There is a low rate of persistent disease. Complete moles are diploid, and all chromosomes are paternal. No embryonic or fetal tissues are present. Among complete moles, 10% to 15% have persistent disease, usually choriocarcinoma. Complete moles subsequently develop choriocarcinoma. Gestational choriocarcinoma is an invasive and frequently metastatic tumor that, in contrast to ovarian choriocarcinoma, is responsive to chemotherapy and curable in most cases. Placental site trophoblastic tumor is an indolent and usually early-stage tumor of intermediate trophoblast that produces hCG and hPL and does not respond well to chemotherapy.





## PREECLAMPSIA/ECLAMPSIA (TOXEMIA OF PREGNANCY)

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The development of hypertension, accompanied by proteinuria and edema in the third trimester of pregnancy, is referred to as *preeclampsia*. This syndrome occurs in 5% to 10% of pregnancies, particularly with first pregnancies in women older than age 35 years. In those severely affected, convulsive seizures may appear, and the symptom complex is then termed *eclampsia*. By long historical precedent, preeclampsia and eclampsia have been referred to as *toxemia of pregnancy*. No blood-borne toxin has ever been identified, however, and so the historically sanctified term (still in use) is clearly a misnomer. Full-blown eclampsia may lead to disseminated intravascular coagulation, with all of its attendant widespread ischemic organ injuries, and so eclampsia is potentially fatal. However, recognition and early treatment of preeclampsia has now made eclampsia and, particularly, fatal eclampsia rare.

The triggering events initiating these syndromes are unknown, but a *basic feature underlying all cases is inadequate maternal blood flow to the placenta secondary to inadequate development of the spiral arteries* of the uteroplacental bed. In the third trimester of normal pregnancy, the musculoelastic walls of the spiral arteries are replaced by a fibrinous material, permitting them to dilate into wide vascular sinusoids. In preeclampsia and eclampsia, the musculoelastic walls are retained and the channels remain narrow. Recent studies suggest that an imbalance between proangiogenic and antiangiogenic factors predates the onset of preeclampsia. Increases in the antiangiogenic factor sFlt1 and reduction in the level of the proangiogenic factor VEGF have been noted. While the exact basis of vascular abnormalities remains unknown, several consequences ensue:

Placental hypoperfusion with an increased predisposition to the development of infarcts  
Reduced elaboration by the trophoblast of the vasodilators prostacyclin, prostaglandin E<sub>2</sub>, and nitric oxide<sup>®</sup>, which in normal pregnancies oppose the effects of renin-angiotensin-hence the hypertension of preeclampsia and eclampsia  
Production by the ischemic placenta of thromboplastic substances such as tissue factor and thromboxane, which probably account for the development of disseminated intravascular coagulation.

### Morphology

The morphologic changes of preeclampsia/eclampsia are variable and depend somewhat on the severity of the toxemic state.

**Placental changes** are most consistent. They include the following:

**Infarcts**, which are a feature of normal pregnancy, are much more numerous in about one-third of women with severe preeclampsia/eclampsia. They may, however, be absent. **Retroplacental hemorrhages** occur in as many as 15% of patients. Placental villi reveal the changes of **premature aging** with villous edema, hypovascularity, and increased production of syncytial epithelial knots. Prominent in well-advanced eclampsia is **acute atherosclerosis** in the spiral arteries, characterized by thickening and fibrinoid necrosis of the vessel wall with focal accumulations of lipid-containing macrophages. Necrosis of these cells releases lipid, which is followed by the accumulation of lymphocytes and macrophages within and about the vessels. Such lesions accentuate the placental ischemia.

accentuate the placental ischemia.

**Multiorgan changes** may be present, reflecting the development of disseminated intravascular coagulation, which is discussed more fully in [Chapter 12](#). Only major findings are considered here. The kidneys are variably affected, depending on the severity of the disseminated intravascular coagulation. Basically, the changes consist of fibrin thrombi within the glomerular capillaries, accompanied by endothelial swelling and possibly mesangial hyperplasia. Focal glomerulitis may ensue. When numerous glomeruli are affected, blood flow to the cortex is reduced, possibly resulting in renal cortical necrosis that may be bilateral and fatal. Microvascular thrombi are also found in the brain, pituitary, heart, and elsewhere. They have the potential of producing focal ischemic lesions accompanied by microhemorrhages.

### *Clinical Features*

Preeclampsia appears insidiously in the 24th to 25th weeks of gestation, with the development of edema, proteinuria, and rising blood pressure. Should the condition evolve into eclampsia, renal function is impaired, the blood pressure mounts, and convulsions may occur. Prompt therapy early in the course aborts the organ changes, with clearance of all abnormalities promptly after delivery or cesarean section.

### **SUMMARY** **Preeclampsia/Eclampsia**

Preeclampsia is characterized by edema, proteinuria, and hypertension in the second to third trimesters of pregnancy. Eclampsia is characterized, in addition, by seizures, and it can be fatal when accompanied by disseminated intravascular coagulation and multiple organ failure. Eclampsia is due to abnormalities in the maternal/placental blood flow, with resultant placental ischemia and infarction and abnormalities in production of vasodilators.







## BREAST

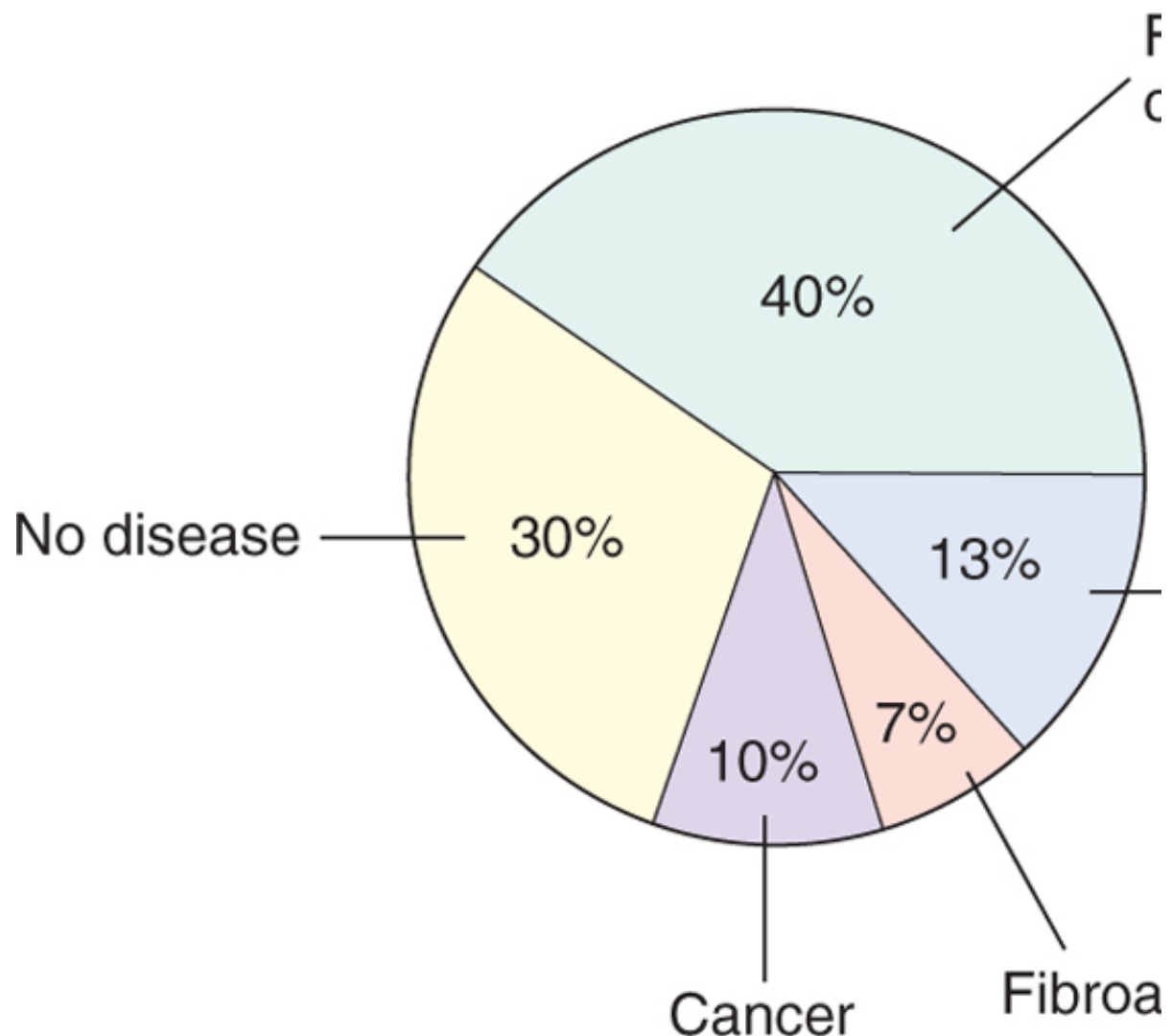
Lesions of the female breast are much more common than lesions of the male breast, which is remarkably seldom affected. These lesions usually take the form of palpable, sometimes painful, nodules or masses. Fortunately, most are innocent, but as is well known, breast cancer was the foremost cause of cancer deaths in women in the United States until 1986, when it was supplanted by carcinoma of the lung. The conditions to be described should be considered in terms of their possible confusion clinically with malignancy. This problem is most acute with fibrocystic change, because it is the most common cause of breast "lumps" and because of the continuing controversy about the association of particular variants with breast carcinoma. However, a significant proportion of women have sufficient irregularity of the "normal" breast tissue to cause them to seek clinical attention ([Fig. 19-23](#)).

Before we turn to the extremely common fibrocystic change, several relatively minor lesions should be mentioned. *Supernumerary nipples or breasts* may be found along the embryonic ridge (milk line). Besides being curiosities, these congenital anomalies are subject to the same diseases that affect the definitive breasts. *Congenital inversion of the nipple* is of significance because similar changes may be produced by an underlying cancer. *Galactocele* is a cystic dilation of an obstructed duct that arises during lactation. Besides being painful "lumps," the cysts may rupture to incite a local inflammatory reaction, which may yield a persistent focus of induration that may arouse suspicion of malignancy.





## FIBROCYSTIC CHANGES



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Figure 19-23 Representation of the findings in a series of women seeking evaluation of a

This designation is applied to a miscellany of changes in the female breast that range from those with an increased risk of breast carcinoma. Some of these alterations (stromal fibrosis and microc "lumps." It is widely accepted that this range of changes is the consequence of an *exaggeration a that occur normally in the menstrual cycle*. Estrogenic therapy and oral contraceptives do not seem to cause alterations; indeed, oral contraceptives may *decrease* the risk.

Traditionally, these breast alterations have been called *fibrocystic disease*; however, physicians have avoided this term. Most of the changes encompassed within the diagnosis of fibrocystic disease have little to do with nodularity; only a small minority represent forms of epithelial hyperplasia that are clinically important. The term *fibrocystic changes* is preferred, since it does not stigmatize the subject with "a disease." Regardless of such terminology, the various patterns of fibrocystic change must be distinguished from cancer, and the distinction between the so-trivial ones can be made by examination of fine-needle aspiration material or more definitively by biopsy. In a somewhat arbitrary manner, the alterations are here subdivided into nonproliferative and proliferative.

in a somewhat arbitrary manner, the alterations are here subdivided into nonproliferative and proliferative. The nonproliferative changes include cysts and/or fibrosis *without* epithelial cell hyperplasia, known as *simple fibrocystic change*; a range of innocuous to atypical duct or ductular epithelial cell hyperplasias and *sclerosing adenosis*; and atypical ductal hyperplasia. The proliferative changes occur throughout the reproductive period of life but may persist after menopause. The various changes, particularly the nonproliferative changes, are found at autopsy in 60% to 80% of women, that they almost constitute physiologic variants.

## Nonproliferative Change

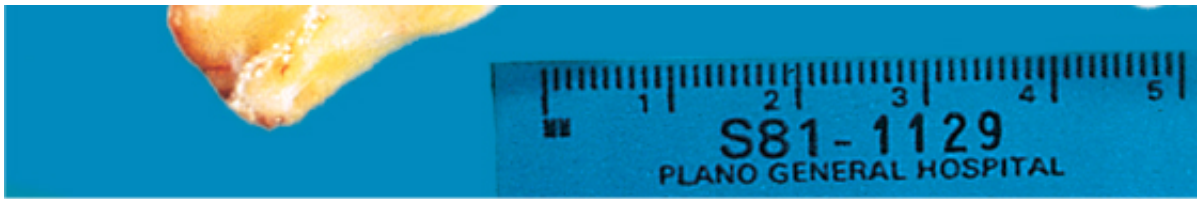
### *Cysts and Fibrosis*

Nonproliferative change is the most common type of alteration, characterized by an increase in fibrous tissue, dilatation of ducts and formation of cysts of various sizes.

#### Morphology

Grossly, a single large cyst may form within one breast, but the disorder is usually bilateral. The involved areas show ill-defined, diffusely increased density and discoloration. Cysts vary from smaller than 1 cm to 5 cm in diameter. Unopened, they are brown to blue; when opened, they are filled with serous, turbid fluid (Fig. 19-24). The secretory products within the cysts may be visible as microcalcifications in mammograms. Histologically, in smaller cysts, the epithelium is usually columnar and is sometimes multilayered in focal areas. In larger cysts it may be flattened and atrophic (Fig. 19-25). Occasionally, mild epithelial proliferation leads to piled-up mucous cells or papillary excrescences. Frequently, cysts are lined by large polygonal cells that have an abundant eosinophilic cytoplasm, with small, round, deeply chromatic nuclei, called **apocrine** cells. These changes are virtually always benign.





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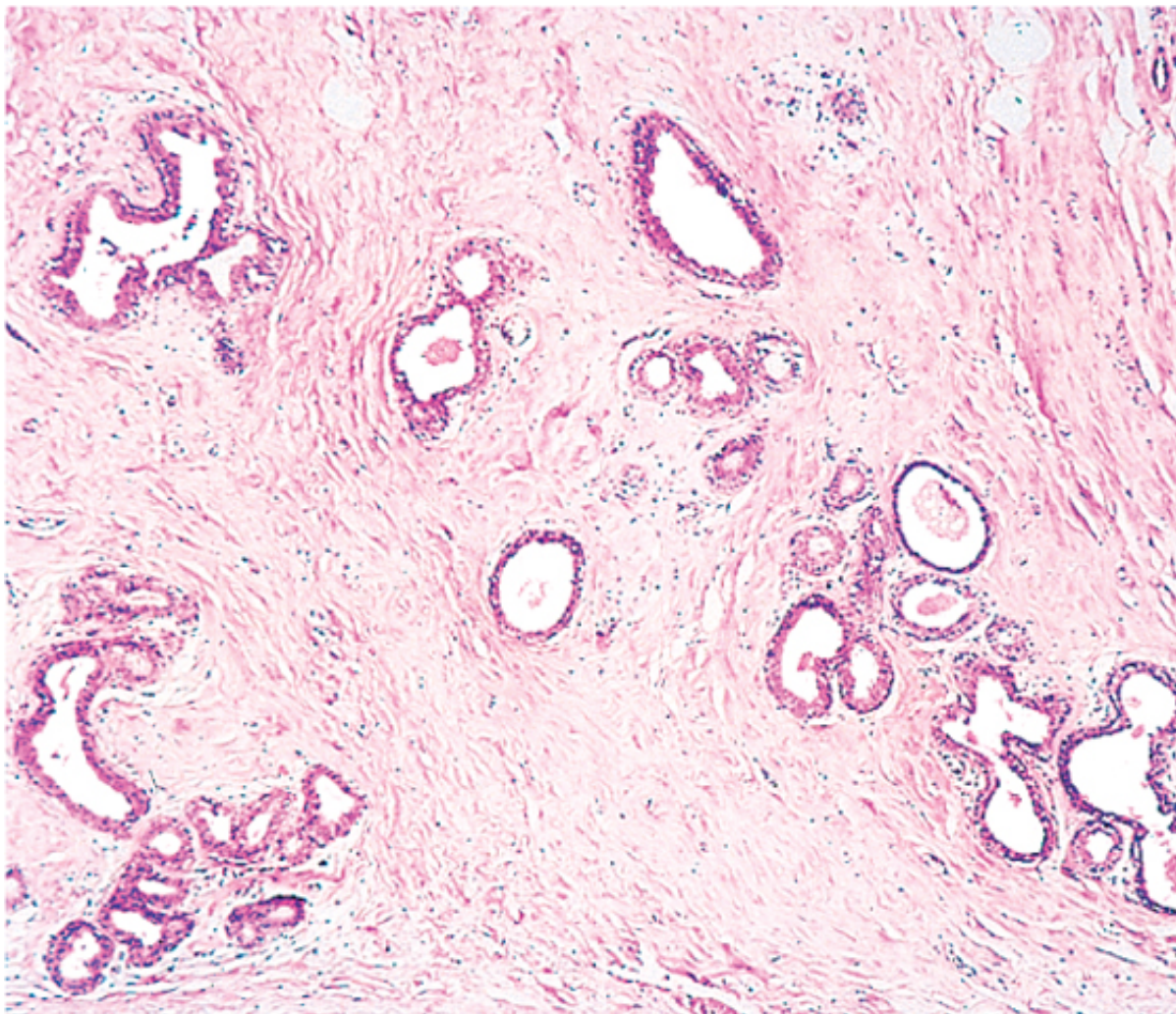
Figure 19-24 Several biopsy specimens showing fibrocystic change of the breast. The scattered, poorly demarcated biopsy specimen at the *lower right* reveals a transected empty cyst; those on the left have unopened blue dome cysts. Pathology, University of Texas Southwestern Medical School, Dallas, TX

The stroma surrounding all forms of cysts is usually compressed fibrous tissue, having lost its normal stromal lymphocytic infiltrate is common in this and all other variants of fibrocystic change.

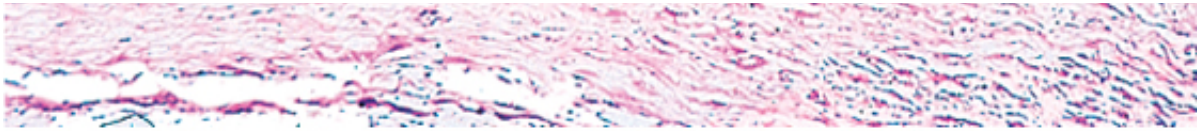
### **Proliferative Change**

#### ***Epithelial Hyperplasia***

The terms *epithelial hyperplasia* and *proliferative fibrocystic change* encompass a range of proliferative changes in the terminal ducts, and sometimes the lobules of the breast. Some of the epithelial hyperplasias are precursors of carcinoma, but at the other end of the spectrum are the more florid atypical hyperplasias that carry a risk commensurate with the severity and atypicality of the changes. The epithelial hyperplasias are often variants of fibrocystic change.







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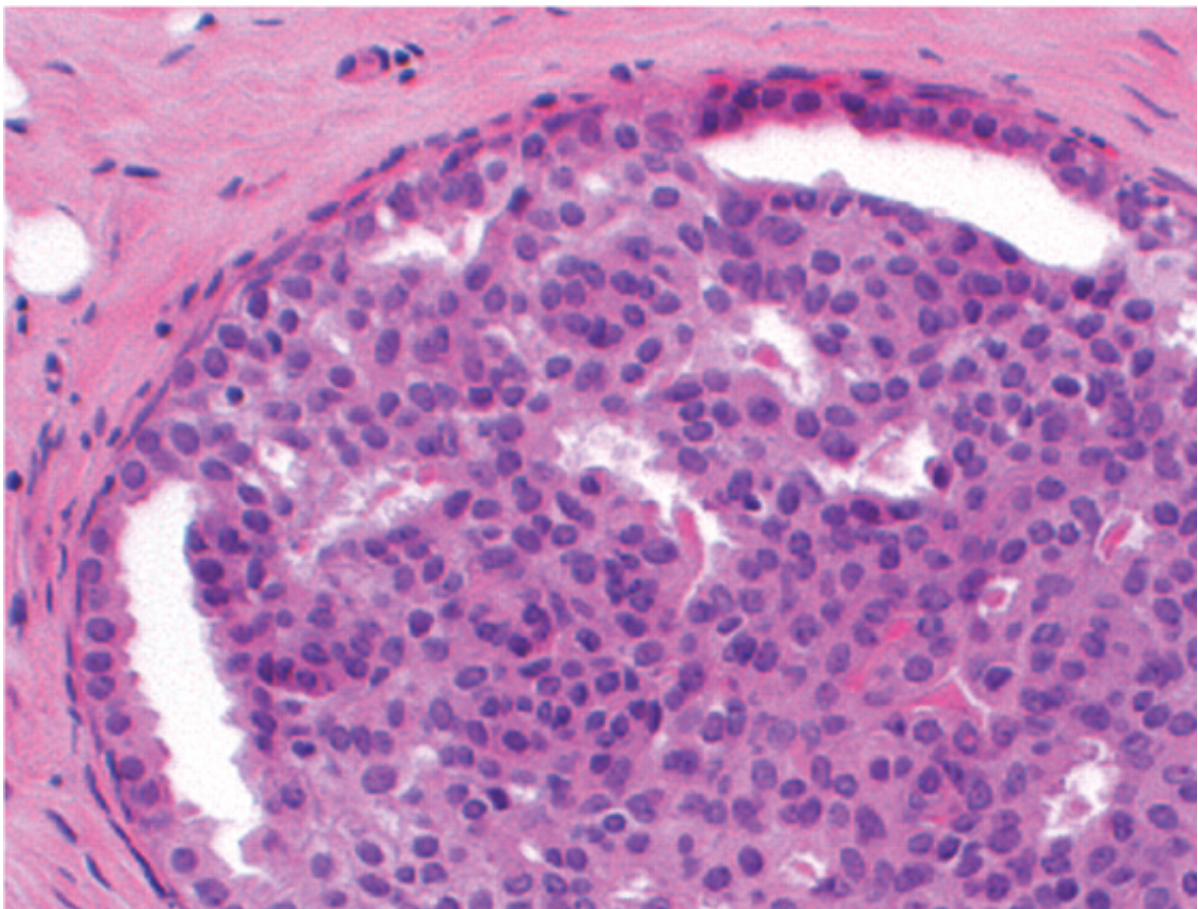
Figure 19-25 Microscopic detail of fibrocystic change of the breast revealing dilation of ducts producing microcysts lined by epithelial cells. (Courtesy of Dr. Kyle Molberg, Department of Pathology, University of Texas South

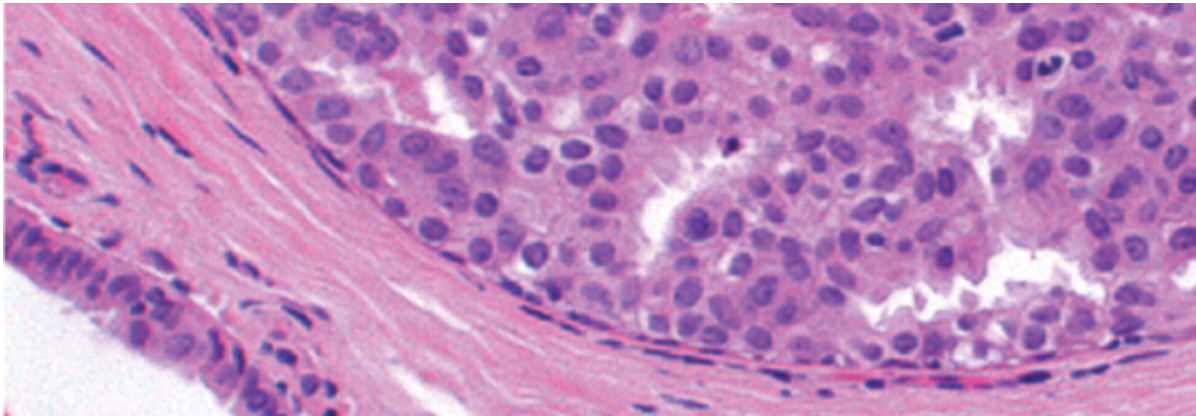
### Morphology

The gross appearance of epithelial hyperplasia is not distinctive and is dominated by cystic changes. Histologically, there is an almost infinite spectrum of proliferative changes. Ductules, or lobules may be filled with orderly cuboidal cells, within which small gaps are discerned (called **fenestrations**) (Fig. 19-26). Sometimes the proliferating epithelium forms small papillary excrescences into the ductal lumen (**ductal papillomatosis**). The degree of change is manifested in part by the number of layers of intraductal epithelial proliferation, ranging from mild to severe.

In some instances the hyperplastic cells become monomorphic with complex architecture, and they have changes approaching those of ductal carcinoma in situ (described later), called **atypical**. The line separating the epithelial hyperplasias without atypia from those with atypia is difficult to define, just as it is difficult to clearly distinguish between atypical hyperplasia and carcinoma. However, these distinctions are important, as will soon become clear.

**Atypical lobular hyperplasia** is the term used to describe hyperplasias that approach ductal carcinoma in situ, but the cells do not fill or distend more than 50% of the acini. Atypical lobular hyperplasia is associated with an increased risk of invasive carcinoma.





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Figure 19-26 Epithelial hyperplasia. The lumen is filled with a heterogeneous population of cells of different morphology, with cells more prominent at the periphery.

Epithelial hyperplasia per se does not often produce a clinically discrete breast mass. Occasionally, on mammography, raising fears about cancer. Such nodularity as may be present usually relates to cystic change; however, florid papillomatosis may be associated with a serous or serosanguineous nipple discharge.

### **Sclerosing Adenosis**

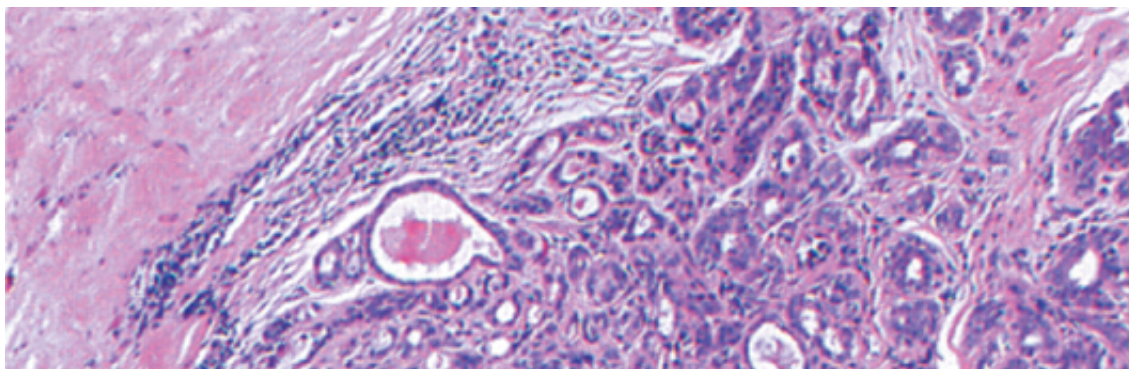
This variant is less common than cysts and hyperplasia, but it is significant because its clinical and histological features are deceptively similar to those of carcinoma. These lesions contain marked intralobular fibrosis and hyperplasia.

#### **Morphology**

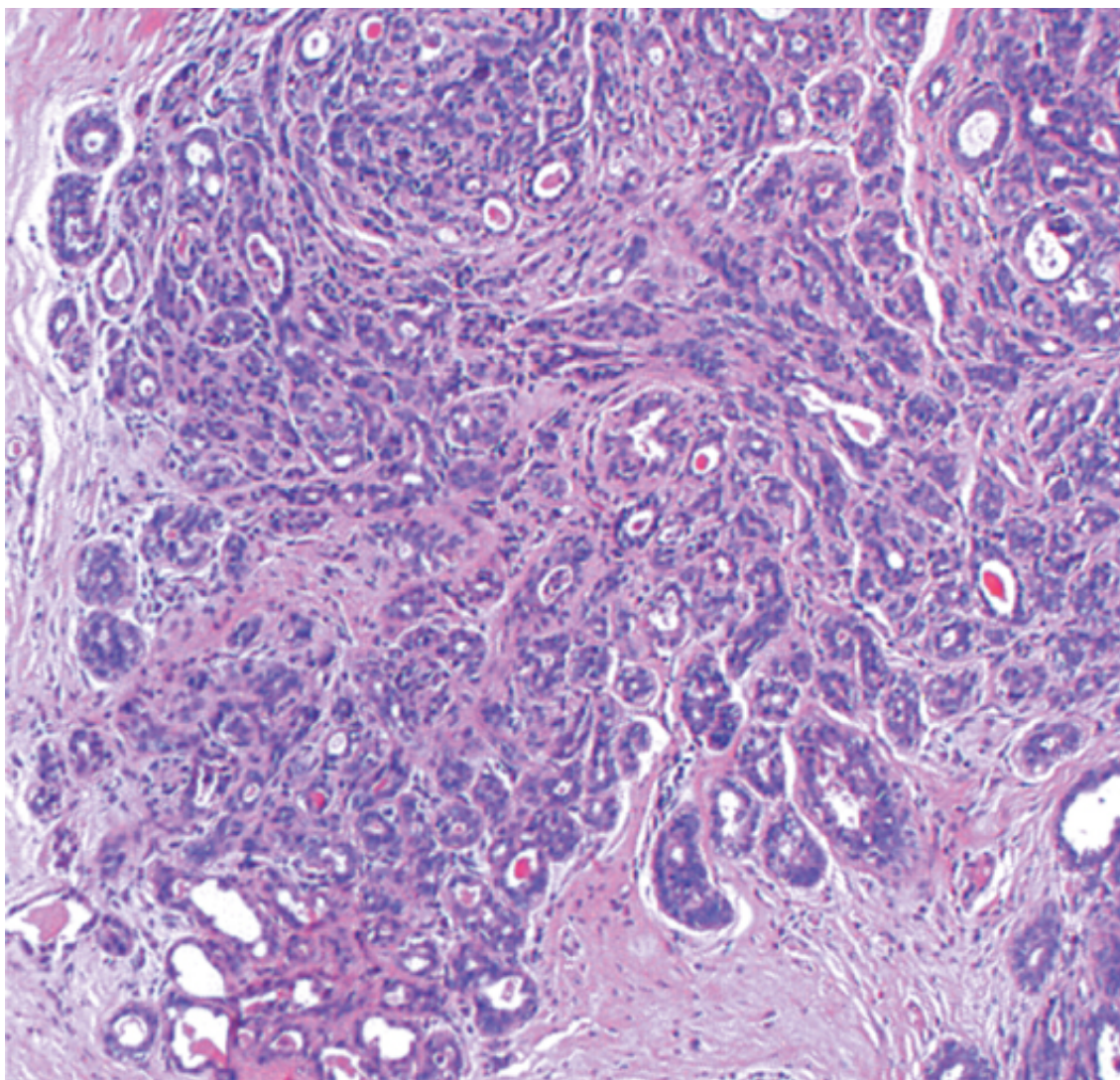
Grossly, the lesion has a hard, rubbery consistency, similar to that of breast cancer. Histologically, sclerosing adenosis is characterized by proliferation of lining epithelial cells and myoepithelial cells within ductules, yielding masses of small gland patterns within a fibrous stroma (Fig. 19-26). Proliferating ductules may be virtually back to back, with single or multiple layers of epithelial cells lining the lumen (hyperplasia). Marked stromal fibrosis, which may compress and distort the ductules, is always associated with the adenosis; hence, the designation **sclerosing adenosis**. The fibrous tissue may completely compress the lumina of the acini and ducts, resulting in **solid cords of cells**. This pattern may then be difficult to distinguish histologically from carcinoma. The presence of double layers of epithelium and the identification of myoepithelial cells are helpful in suggesting a benign diagnosis.

Although sclerosing adenosis is sometimes difficult to differentiate clinically and histologically from carcinoma, it is associated with a minimally increased risk of progression to carcinoma.

### **Relationship of Fibrocystic Changes to Breast Carcinoma**







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Figure 19-27 Sclerosing adenosis. The involved terminal duct lobular unit is enlarged, and the acini are compressed. Calcifications are often present within the lumens. Although this lesion is frequently mistaken for an invasive carcinoma, it has a swirling pattern, and the outer border is usually well circumscribed.

The relationship of fibrocystic changes to breast carcinoma is controversial. Only some reasonable conclusions are possible. Clinically, although certain features of fibrocystic change tend to distinguish it from cancer, the distinction is through biopsy and histologic examination. With respect to the relationship of the various changes to cancer, the statements below currently represent the best-informed opinion:

*Minimal or no increased risk of breast carcinoma:* fibrosis, cystic changes (microscopic or macroscopic), hyperplasia, fibroadenoma. *Slightly increased risk (1.5-2 times):* moderate to florid hyperplasia, papillomatosis, sclerosing adenosis. *Significantly increased risk (5 times):* atypical hyperplasia (hyperplasia seen on biopsies). Proliferative lesions may be multifocal, and the risk of subsequent carcinoma extends to the contralateral breast. *breast cancer may increase the risk in all categories (e.g., to ~10-fold with atypical hyperplasia).*

Fortunately, most women who have lumps related to fibrocystic change can be reassured that the lump is not cancer. The need to differentiate among the many variants and the grounds for dissatisfaction with the classification of fibrocystic changes or, even worse, *fibrocystic disease* are apparent.

## SUMMARY

## Fibrocystic Changes

Classified as nonproliferative cystic lesions or proliferative lesions. Proliferative lesions include epithelial proliferations of ducts and lobules, with or without features of atypia. Proliferation of terminal ducts, sometimes associated with fibrosis (sclerosing adenosis), hyperplasia of ductular or lobular epithelium is associated with a five-fold increase in the risk of developing carcinoma; when associated with a family history of breast carcinoma, the risk is increased tenfold.



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## INFLAMMATIONS

Inflammations of the breast are uncommon and during the acute stages usually cause pain and tenderness in the involved areas. Included in this category are several forms of mastitis and traumatic fat necrosis, none of which are associated with increased risk of cancer.

Acute mastitis develops when bacteria gain access to the breast tissue through the ducts; when there is inspissation of secretions; through fissures in the nipples, which usually develop during the early weeks of nursing; or from various forms of dermatitis involving the nipple.

### **Morphology**

#### **Staphylococcal infections induce single or multiple abscesses**

accompanied by the typical clinical acute inflammatory changes. They are usually small, but when sufficiently large they may heal with residual foci of scarring that are palpable as localized areas of induration.

Streptococcal infections generally spread throughout the entire breast, causing pain, marked swelling, and breast tenderness. Resolution of these infections rarely leaves residual areas of induration.

*Mammary duct ectasia (periductal or plasma cell mastitis)* is a nonbacterial chronic inflammation of the breast associated with inspissation of breast secretions in the main excretory ducts. Ductal dilation with ductal rupture leads to reactive changes in the surrounding breast substance. It is an uncommon condition, usually encountered in women in their 40s and 50s who have borne children.

### **Morphology**

Usually the inflammatory changes are confined to an area drained by one or several of the major excretory ducts of the nipple. There is increased firmness of the tissue, and on cross-section dilated ropelike ducts are apparent from which thick, cheesy secretions can be extruded.

Histologically, the ducts are filled by granular debris, sometimes containing leukocytes, principally lipid-laden macrophages. The lining epithelium is generally destroyed. **The most distinguishing features are the prominence of a lymphocytic and plasma cell infiltration and occasional granulomas in the periductal stroma.**

Mammary duct ectasia is of principal importance because it leads to induration of the breast substance and, more significantly, to retraction of the skin or nipple, mimicking the changes caused by some carcinomas.

*Traumatic fat necrosis* is an uncommon and innocuous lesion that is significant only because it produces a mass. Most, but not all, women with this condition report some antecedent trauma to the breast.

### **Morphology**

During the early stage of traumatic fat necrosis, the lesion is small, often tender, rarely more than 2 cm in diameter, and sharply localized. It consists of a central focus of necrotic fat cells surrounded by neutrophils and lipid-filled macrophages, which is later enclosed by fibrous tissue and mononuclear leukocytes. Eventually the focus is replaced by scar tissue, or the debris becomes encysted within the scar. Calcifications may develop in either the scar or cyst wall.

may develop in either the cornea or eye wall.



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## TUMORS OF THE BREAST

Tumors are the most important lesions of the female breast. Although they may arise from either (it is the latter that give rise to the common breast neoplasms. Here we will describe fibroadenoma, carcinoma, and carcinoma of the breast.

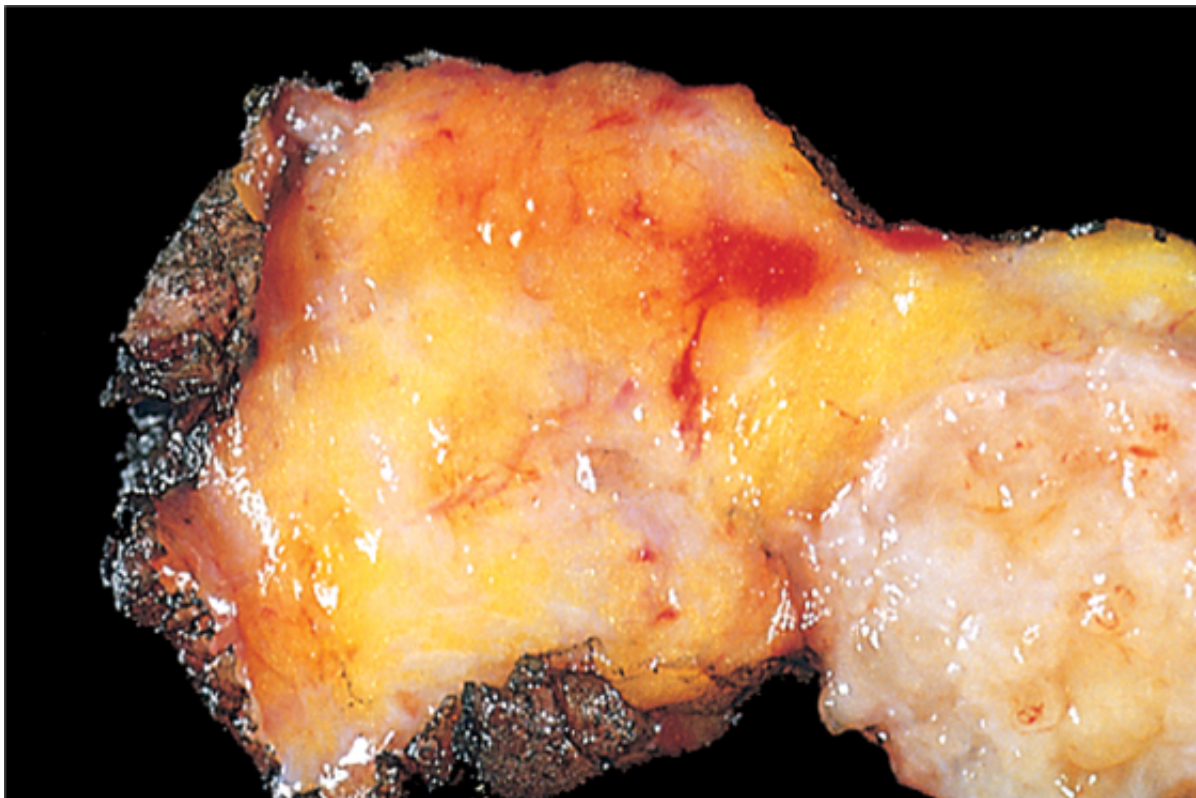
### Fibroadenoma

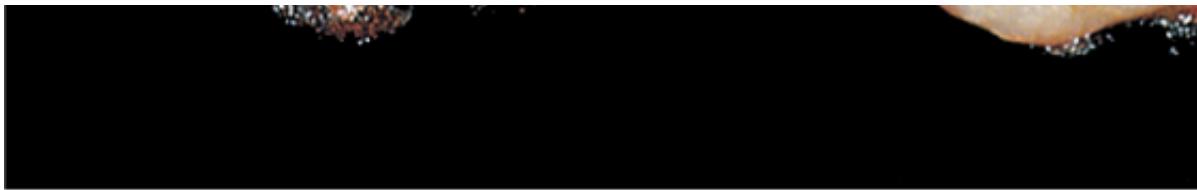
Fibroadenoma is by far the most common benign neoplasm of the female breast. An absolute or relative thought to contribute to its development, and indeed similar lesions may appear with fibrocystic changes. Fibroadenomas usually appear in young women; the peak incidence is in the third decade of life.

#### Morphology

The fibroadenoma occurs as a discrete, usually solitary, freely movable nodule, 1 to 5 cm in size. Rarely, multiple tumors are encountered and, equally rarely, they may exceed 10 cm in size (**fibroadenoma**). Whatever their size, they are usually easily "shelled out." Grossly, tan-white color on cut section, punctuated by softer yellow-pink specks representing fat (Fig. 19-28). Histologically there is a loose fibroblastic stroma containing ductlike, epithelial spaces of various forms and sizes. These ductlike or glandular spaces are lined with single or double layers of cells that are regular and have a well-defined, intact basement membrane. Although in some cases the spaces are open, round to oval, and fairly regular (**pericanalicular fibroadenoma**), in others they are crowded by extensive proliferation of the stroma, so that on cross-section they appear as slitlike structures (**intracanalicular fibroadenoma**) (Fig. 19-29).

### Clinical Features





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Figure 19-28 Fibroadenoma. A rubbery, white, well-circumscribed mass is clearly demarcated from the surrounding normal tissue. The mass does not contain adipose tissue and therefore appears denser than the surrounding normal tissue.

Clinically, fibroadenomas usually present as solitary, discrete, movable masses. They may enlarge during pregnancy. After menopause they may regress and calcify. Cytogenetic studies reveal that the stroma represents the neoplastic element of these tumors. The basis of ductal proliferation is not clear; possible growth factors that induce proliferation of epithelial cells. Fibroadenomas almost never become malignant.

### Phyllodes Tumor

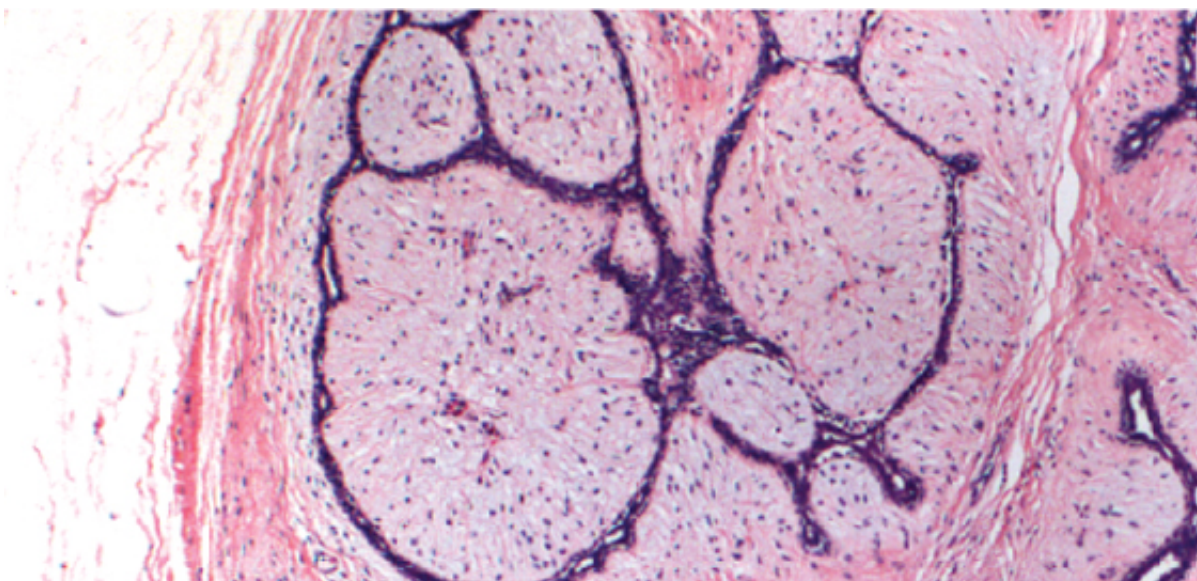
These tumors are much less common than fibroadenomas and are thought to arise from the periductal stroma. They may be small (3-4 cm in diameter), but most grow to large, possibly massive sizes. They become lobulated and cystic; because on gross section they exhibit leaflike clefts and slits, they have the name "leaflike" tumors. In the past they had the tongue-tangling name *cystosarcoma phyllodes*, and they are usually benign. The most ominous change is the appearance of increased stromal cellularity, which is accompanied by rapid increase in size, usually with invasion of adjacent breast tissue by malignant cells. Benign lesions are cured by excision; malignant lesions may recur, but they also tend to remain localized. In 15% of cases, metastasize to distant sites.

### Intraductal Papilloma

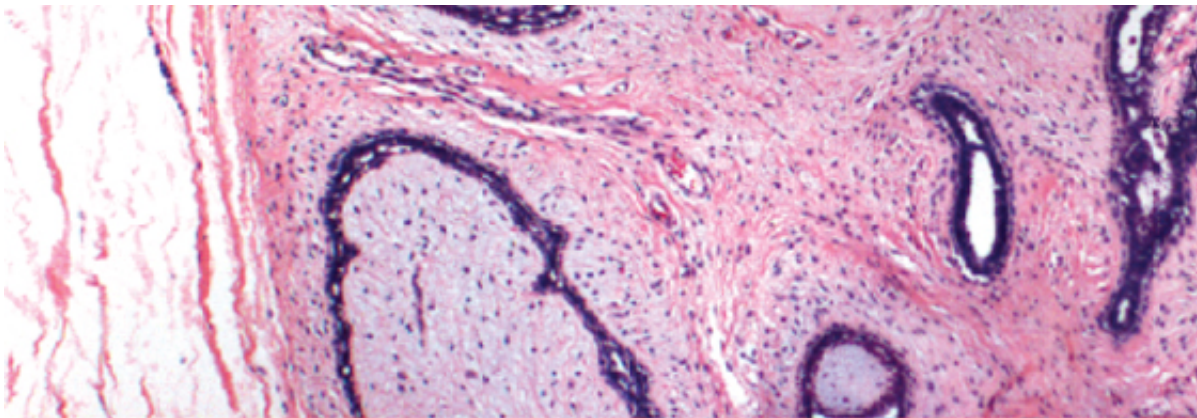
This is a neoplastic papillary growth within a duct. Most lesions are solitary, found within the principal duct. They present clinically as a result of (1) the appearance of serous or bloody nipple discharge, (2) the presence of a palpable mass, or (3) rarely, nipple retraction.

#### Morphology

The tumors are usually solitary and less than 1 cm in diameter, consisting of delicate papillae within a dilated duct or cyst. Histologically, they are composed of multiple papillae, each with a central fibrovascular tissue axis covered by cuboidal or cylindrical epithelial cells that are frequently double-layered. The inner layer is the epithelial layer overlying a myoepithelial layer.







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Figure 19-29 Fibroadenoma. The lesion consists of a proliferation of intralobular stroma surrounding and often pushing against the ductal border is sharply delimited from the surrounding tissue.

In some cases there are multiple papillomas in several ducts or *intraductal papillomatosis*. These whereas the solitary papilloma almost always remains benign. Papillary carcinoma must also be a component and shows either severe cytologic atypia or monotonous ductal epithelium.

### Carcinoma

No cancer is more feared by women than carcinoma of the breast, and for good reason. In the United States, the American Cancer Society that 212,920 new invasive breast cancers will be discovered in women making this scourge second only to lung cancer as a cause of cancer death in women. The data on diagnosis and treatment, almost one-fourth of women who develop these neoplasms will die of the disease. The data emphasize that although the lifetime risk is one in eight for women in the United States, 75% of women are age 50. Only 5% are younger than the age of 40. For unknown reasons (possibly related in some cases to mammography), there has been an increase in the incidence of breast cancer throughout the world. The incidence is holding steady at about 1% a year, when it started to climb in 1980 to 3% to 4% a year. Fortunately, the incidence is 111 cases per 100,000 women. Understandably, then, there has been intense study of the possible means to diagnose it early enough to permit cure.

### Epidemiology and Risk Factors

A large number of risk factors have been identified that modify a woman's likelihood of developing breast cancer. The risk factors are divided into well-established and less well-established groups and indicates, where possible, the relative risk. Comments about some of the more important risk factors follow.

Table 19-4. Breast Cancer Risk Factors

Factor	Relative Risk
<b>Well-Established Influences</b>	
Geographic factors	Varies in different countries
Age	Increases with age
Family history	
First-degree relative with breast cancer	1.2-3.0
Premenopausal	3.1
Premenopausal and bilateral	8.5-9.0
Postmenopausal	1.5
Postmenopausal and bilateral	4.0-5.4
Menstrual history	
Age at menarche <12yr	1.2

Age at menarche <12yr	1.5
Age at menopause >55yr	1.5-2.0
Pregnancy	
First live birth from ages 25 to 29yr	1.5
First live birth after age 30yr	1.9
First live birth after age 35yr	2.0-3.0
Nulliparous	3.0
Benign breast disease	
Proliferative disease without atypia	1.6
Proliferative disease with atypical hyperplasia	>2.0
Lobular carcinoma in situ	6.9-12.0
<b>Less Well-Established Influences</b>	
Exogenous estrogens	
Oral contraceptives	
Obesity	
High-fat diet	
Alcohol consumption	
Cigarette smoking	

Extensively modified from Bilimoria MM, Morrow M: The women at increased risk for breast cancer: evaluation and management st

### Geographic Variations

There are surprising differences among countries in the incidence and mortality rates of breast cancer. The rates are significantly higher in North America and northern Europe than in Asia and Africa. For example, the rates are 10 times higher in the United States than in Japan. These differences seem to be environmental rather than genetic. Women who migrate from low-incidence locales to high-incidence areas tend to acquire the rates of their adoptive countries. Reproductive patterns, and nursing habits are thought to be involved.

### Age

Breast cancer is uncommon in women younger than age 30. Thereafter, the risk steadily increases. The upward slope of the curve almost plateaus after age 50.

### Genetics and Family History

About 5% to 10% of breast cancers are related to specific inherited mutations. Women are more likely to develop breast cancer if they develop breast cancer before menopause, have bilateral cancer, have cancer of the ovary, have a significant family history (i.e., multiple relatives affected before menopause), or belong to certain ethnic groups. About 10% of women with hereditary breast cancer have mutations in gene *BRCA1* (on chromosome 17q21.31) and about 40% have mutations in *BRCA2* (on chromosome 13q12-13). These are large, complex genes that do not exist in other known genes. Although their exact role in carcinogenesis and their relative specificity for breast cancer are thought to function in DNA repair (Chapter 6). They act as tumor suppressor genes. One allele is inactive or defective—one caused by a germ-line mutation and the second by a subsequent somatic mutation. However, it is complicated by the hundreds of different mutant alleles, only some of which confer high penetrance, the age at cancer onset, and the association with susceptibility to other types of cancer. However, most carriers will develop breast cancer by the age of 70 years, as compared with only 10% for women with no mutation. The role of these genes in nonhereditary sporadic breast cancer is less clear, because mutations are infrequent in these tumors. It is possible that other mechanisms, such as methylation of regulatory regions, are involved in sporadic cancer. Less common genetic diseases associated with breast cancer are the Li-Fraumeni syndrome (caused by mutations in *p53*; Chapter 6), Cowden disease (caused by germ-line mutations in *PTEN*; discussed in the context of the ataxia-telangiectasia gene (Chapter 6).

### Other Risk Factors

**Prolonged exposure to exogenous estrogens** postmenopausally, known as hormone replacement therapy, is associated with an increased risk of breast cancer. However, according to recent studies, relatively short-term use of combined

therapy is associated with an increased risk of breast cancer, diagnosis at a more advanced stage, and fewer mammograms. Because the 2002 Women's Health Initiative report suggested greater harm than benefit from hormone therapy, there has been a precipitous decline in estrogen and progestin use and a serious reevaluation of hormone therapy.

*Oral contraceptives* have also been suspected of increasing the risk of breast cancer. Once again, newer formulations of balanced low doses of combined estrogens and progestins seem to be safe. There is now solid evidence that birth control pills do not increase the risk of breast cancer even in women who have a family history of breast cancer.

*Ionizing radiation* to the chest increases the risk of breast cancer. The magnitude of the risk depends on the dose of radiation, the duration of exposure, and age. Only women irradiated before age 30, during breast development, seem to be at increased risk. Women irradiated for Hodgkin lymphoma in their teens and 20s develop breast cancer, but the risk is not as high as in women who received higher doses of radiation. The low doses of radiation associated with mammographic screening have little, if any, effect. Any possible effect is compensated for by the demonstrated benefits of earlier detection of breast cancer.

*Many other less well-established risk factors*, such as obesity, alcohol consumption, and a diet high in fat, have been associated with the development of breast cancer on the basis of population studies. Obesity is a recognized risk factor for breast cancer.

### *Pathogenesis*

As is the case with all cancers, the cause of breast cancer remains unknown. However, three sets of factors are involved: (1) genetic changes, (2) hormonal influences, and (3) environmental variables.

### *Genetic Changes*

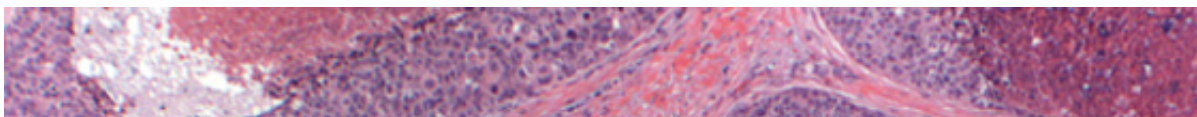
In addition to those producing the well-established familial syndromes mentioned earlier, genetic changes are involved in the genesis of sporadic breast cancer. As with most other cancers, mutations affecting proto-oncogenes and tumor suppressor genes contribute to the oncogenic transformation process. Among the best characterized is the *HER2/neu* oncogene, which has been found to be amplified in up to 30% of invasive breast cancers. This gene encodes a growth factor receptor family, and its overexpression is associated with a poor prognosis. Analogously, alterations in the *p53* tumor suppressor gene have also been reported in some human breast cancers. Mutations of the well-known tumor suppressor gene *p16* have also been reported. A large number of genes including the estrogen receptor may be inactivated by promoter hypermethylation. Genetic alterations are involved in the sequential transformation of a normal epithelial cell into a cancer cell. One of the most striking results from genetic analyses of breast cancers is that it is heterogeneous at the molecular level. This has led to the classification of breast cancer into five subtypes: luminal A (estrogen receptor positive), luminal B (estrogen receptor positive, *HER2/neu* positive), HER2-enriched (estrogen receptor negative, *HER2/neu* positive), basal-like (estrogen receptor negative, *HER2/neu* negative), and normal-like (estrogen receptor positive, *HER2/neu* negative). These subtypes are associated with different outcomes.

### *Hormonal Influences*

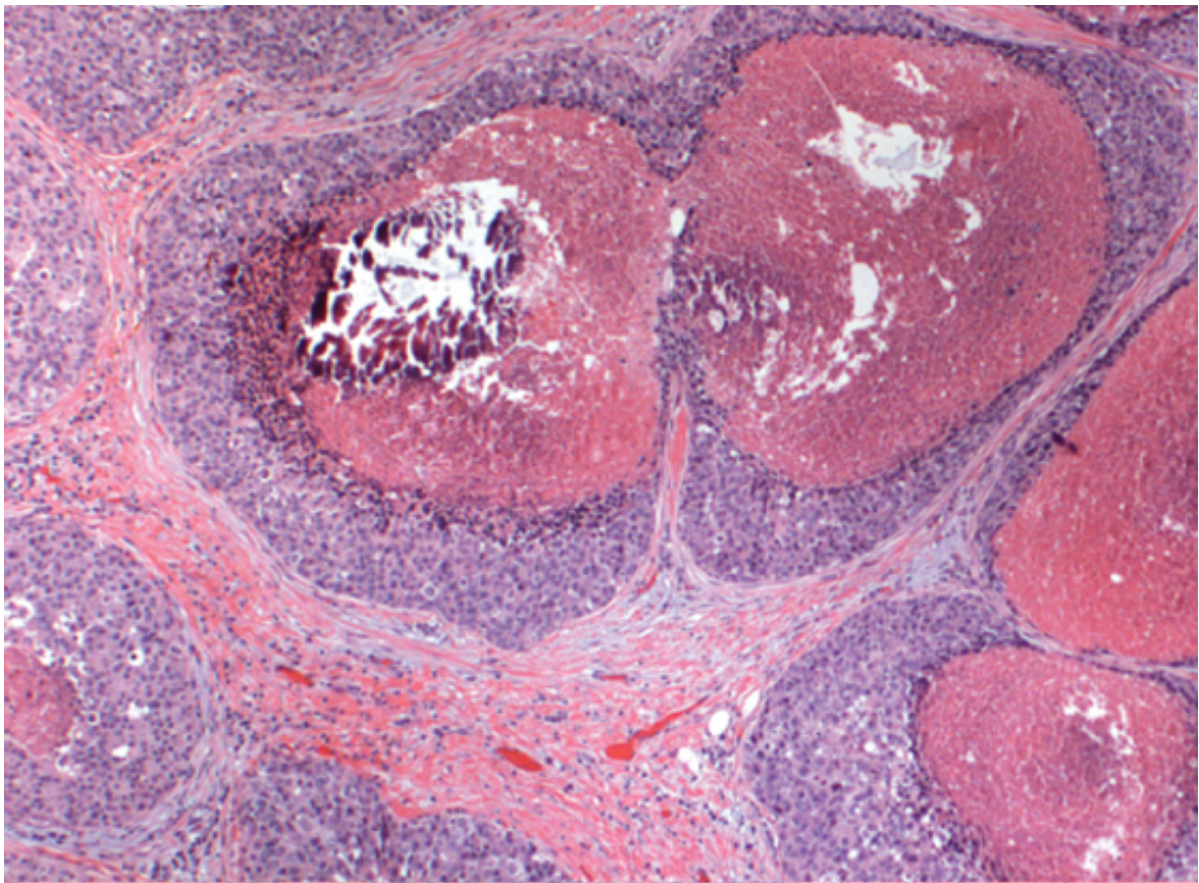
Endogenous estrogen excess, or more accurately, hormonal imbalance, clearly has a significant role in the development of breast cancer. Factors that imply increased exposure to estrogen, such as long duration of reproductive life, nulliparity, and late age at birth of first child, are associated with an increased risk of breast cancer (see Table 19-4). Functioning ovarian tumors that elaborate estrogens are associated with an increased risk of breast cancer in postmenopausal women. Estrogens stimulate the production of growth factors by normal breast epithelial cells. It is hypothesized that the estrogen and progesterone receptors normally present in breast epithelial cells, may interact with growth promoters, such as transforming growth factor  $\alpha$ , platelet-derived growth factor, and others, to create an autocrine mechanism of tumor development.

### *Environmental Variables*

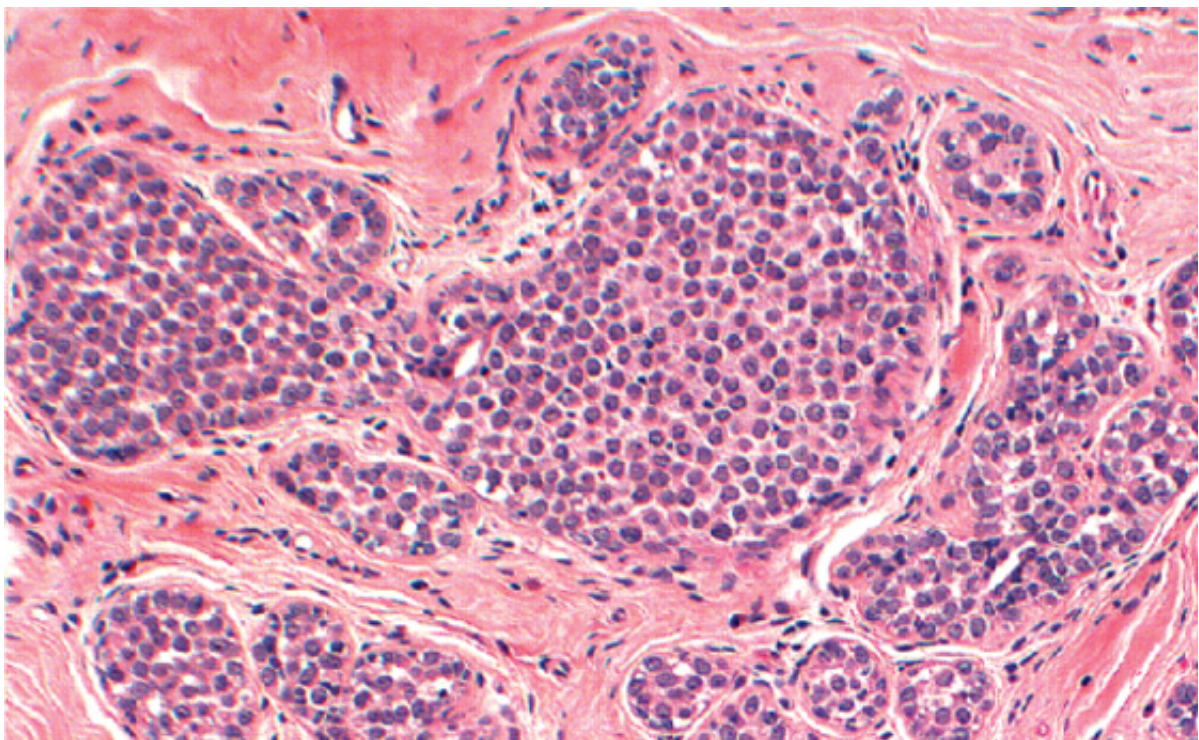
Environmental influences are suggested by the variable incidence of breast cancer in genetically identical twins and by differences in prevalence, as discussed earlier. Other important environmental variables include diet, alcohol consumption, and obesity, as described earlier.



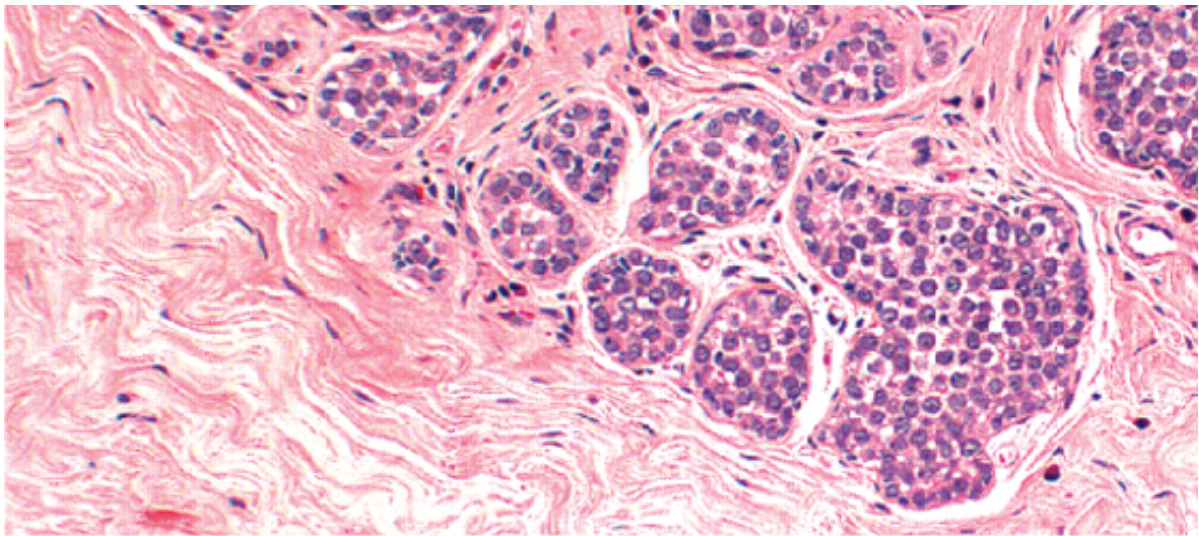




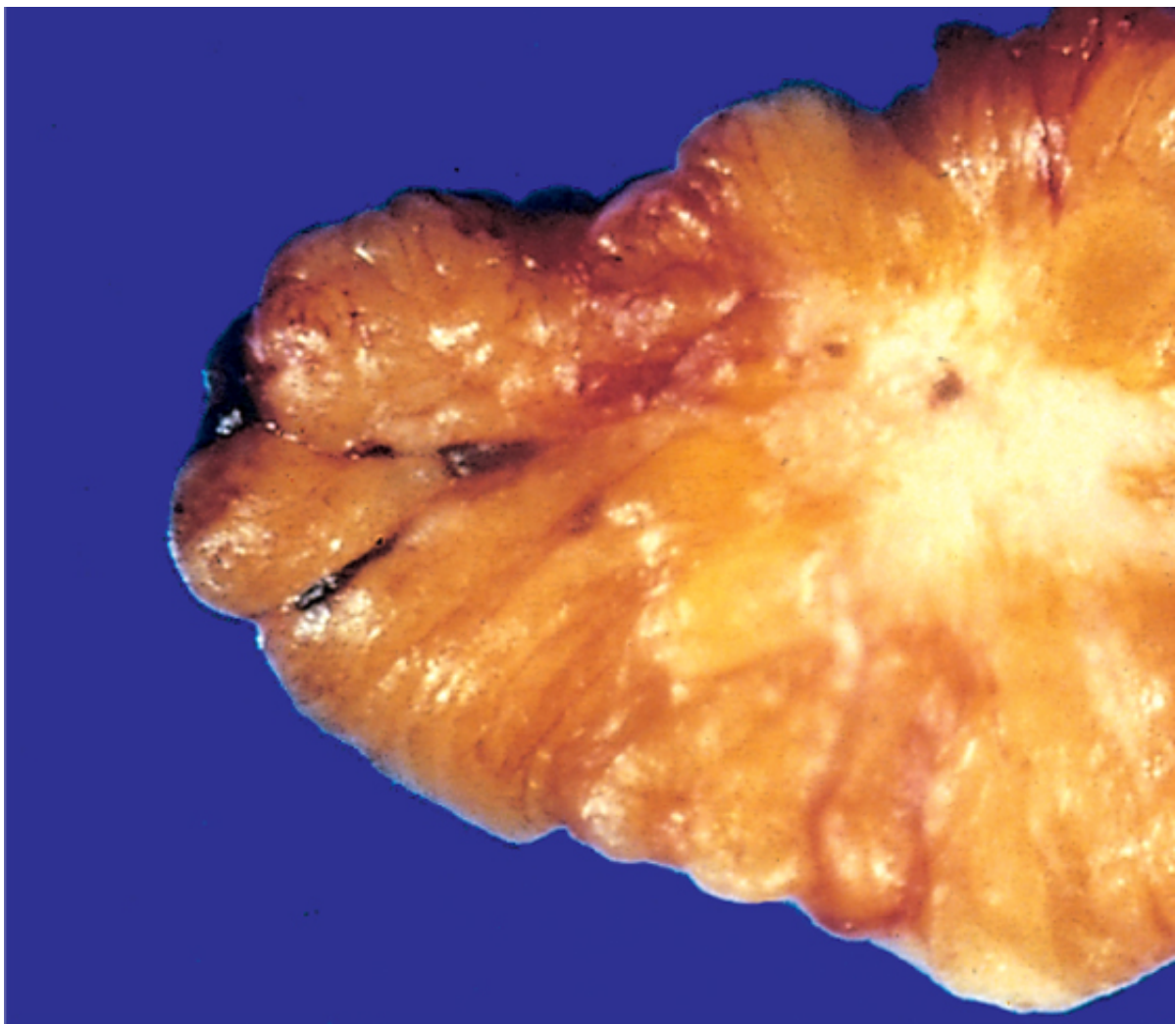
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 Figure 19-30 Comedo DCIS fills several adjacent ducts and is characterized by large central zones of necrosis, which are frequently detected as radiologic calcifications.







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Figure 19-31 Lobular carcinoma in situ. A monomorphic population of small, rounded, loosely cohesive cells fills a lobular architecture can still be recognized.



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Figure 19-32 A cut section of an invasive ductal carcinoma of the breast. The lesion is retracted, infiltrating the surrounding stroma, and is hard on palpation.

### Morphology

Cancer of the breast affects the left breast slightly more often than the right. About 10% of breast cancer have bilateral primary tumors or sequential lesions in the same breast. The distribution of breast cancer within the breast are:

Upper outer quadrant
Central portion
Lower outer quadrant
Upper inner quadrant
Lower inner quadrant

Breast cancers are classified into those that have not penetrated the limiting basement membrane (noninvasive) and those that have (invasive). The chief forms of carcinoma of the breast are as follows:

- A. Noninvasive
  1. Ductal carcinoma in situ (DCIS; intraductal carcinoma)
  2. Lobular carcinoma in situ (LCIS)
- B. Invasive (infiltrating)
  1. Invasive ductal carcinoma ("not otherwise specified")
  2. Invasive lobular carcinoma
  3. Medullary carcinoma
  4. Colloid carcinoma (mucinous carcinoma)
  5. Tubular carcinoma
  6. Other types

Of these, invasive ductal carcinoma is by far the most common. Because it usually infiltrates the surrounding stroma, it is also referred to as **scirrhous carcinoma**.

**Noninvasive (in Situ) Carcinoma (including Paget Disease).** There are two types of noninvasive carcinoma: DCIS and LCIS. Morphologic studies have shown that both usually arise within the lobular unit. DCIS tends to fill, distort, and unfold involved lobules and thus appears as solid nests of cells. In contrast, LCIS usually expands but does not alter the underlying lobular architecture. Both are confined by a basement membrane and do not invade into stroma or lymphovascular spaces.

**DCIS** has a wide variety of histologic appearances. Architectural patterns are often comedo, cribriform, papillary, micropapillary, and clinging types. Necrosis may be present in the comedo type. Nuclear appearance tends to be uniform in a given case, and ranges from low-grade (low nuclear grade) to pleomorphic (high nuclear grade). The **comedo** subtype is distinguished by cells with high-grade nuclei distending spaces with extensive central necrosis (the term comedo derives from the toothpaste-like necrotic tissue that can be extruded from transected comedo cysts under pressure). Calcifications are frequently associated with DCIS, as a result of either cellular debris or secretory material. The incidence of DCIS markedly increases from less than 5% in unselected populations up to 40% of those screened by mammography, primarily as a result of the detection of calcifications. Currently, DCIS only rarely presents as a palpable or radiologically detectable mass; if detection is delayed, a palpable mass or nipple discharge may develop. The cells in DCIS tumors express estrogen and, less often, progesterone receptors. The prognosis for DCIS is excellent, with over 97% long-term survival after simple mastectomy. Some women develop distant recurrence; such cases usually have extensive high-nuclear-grade DCIS and small areas of invasion. At least one-third of women with small areas of untreated DCIS will eventually develop invasive carcinoma. When invasive cancer does develop, it tends to arise in the same breast and quadrant as the earlier DCIS. Current treatment strategies attempt to prevent progression to invasive cancer.

breast and quadrant as the earlier DCIS. Current treatment strategies attempt to use surgery and radiation. Treatment with the anti-estrogenic tamoxifen may also decrease recurrence. Treatment with aromatase inhibitors for postmenopausal women is being examined.

**Paget disease of the nipple** is caused by the extension of DCIS up to the lactiferous ducts and contiguous skin of the nipple. The malignant cells disrupt the normal epidermal barrier, and extracellular fluid to be extruded onto the surface. The clinical appearance is usually a red, scaly exudate over the nipple and areolar skin. In about half of cases, an underlying invasive carcinoma may be present. Prognosis is based on the underlying carcinoma and is not worsened by the Paget disease.

**LCIS**, like the low-nuclear-grade DCIS and unlike high-nuclear-grade DCIS, has cells that are monomorphic with bland, round nuclei and occur in loosely cohesive clusters (Fig. 19-31). Intracellular mucin vacuoles (signet ring cells) are common. LCIS is usually an incidental finding, and, unlike DCIS, it does not form masses and is only rarely associated with invasive carcinoma. Therefore, the incidence of LCIS is almost unchanged in mammographically screened women. Approximately one-third of women with LCIS will eventually develop invasive carcinoma. **Subsequent invasive carcinomas arise in either breast at significant frequency.** These cancers will be of lobular type (as compared with ~10% of cancers in women with DCIS of lobular carcinoma), but most are of no special type. Thus, **LCIS is both a marker of developing breast cancer in either breast and a direct precursor of some cancers.** It requires either close clinical and radiologic follow-up of both breasts or bilateral prophylactic mastectomy.

**Invasive (Infiltrating) Carcinoma.** The morphology of the subtypes of invasive carcinoma is followed by the clinical features of all.

**Invasive ductal carcinoma** is a term used for all carcinomas that cannot be subdivided into the specialized types described below and does not indicate that this tumor specifically involves the ductal system. **Carcinomas of "no special type" or "not otherwise specified" are synonymous with invasive ductal carcinomas.** The majority (70% to 80%) of cancers fall into this group. This type of carcinoma is not associated with DCIS, but rarely LCIS is present. Most ductal carcinomas produce a mass that replaces normal breast fat (resulting in a mammographic density) and forms a mass (Figs. 19-32 and 19-33). The microscopic appearance is quite heterogeneous, ranging from well-developed tubule formation and low-grade nuclei to tumors consisting of sheets of cells. Tumor margins are usually irregular (Fig. 19-34) but are occasionally pushing and circumscribed. Lymphovascular spaces or along nerves may be seen. Advanced cancers may cause retraction of the nipple, or fixation to the chest wall. About two-thirds express estrogen receptors, and about one-third overexpress HER2/NEU.

**Inflammatory carcinoma** is defined by the clinical presentation of an enlarged, swollen breast, usually without a palpable mass. The underlying carcinoma is generally poorly differentiated and diffusely invades the breast parenchyma. The blockage of numerous dermal lymphatics results in the clinical appearance. True inflammation is minimal or absent. Most of these cancers have distant metastases, and the prognosis is extremely poor.

**Invasive lobular carcinoma** consists of cells morphologically identical to the cells of LCIS. In some cases are associated with adjacent LCIS. The cells invade individually into stroma as single cells, strands or chains. Occasionally they surround cancerous or normal-appearing acini, forming a pattern called bull's-eye pattern. Although most present as palpable masses or mammographically detectable masses, a significant subgroup may have a diffusely invasive pattern without a desmoplastic reaction. Lobular carcinomas, more frequently than ductal carcinomas, metastasize to the lung, pleural fluid, serosal surfaces, gastrointestinal tract, ovary and uterus, and bone marrow. They are also more frequently multicentric and bilateral (10% to 20%). Almost all of these cancers express estrogen hormone receptors, but HER2/NEU overexpression is very rare or absent. These tumors constitute about 20% of all breast carcinomas.

**Medullary carcinoma** is a rare subtype of carcinoma constituting fewer than 1% of all breast carcinomas. It consists of sheets of large anaplastic cells with pushing, well-circumscribed borders.

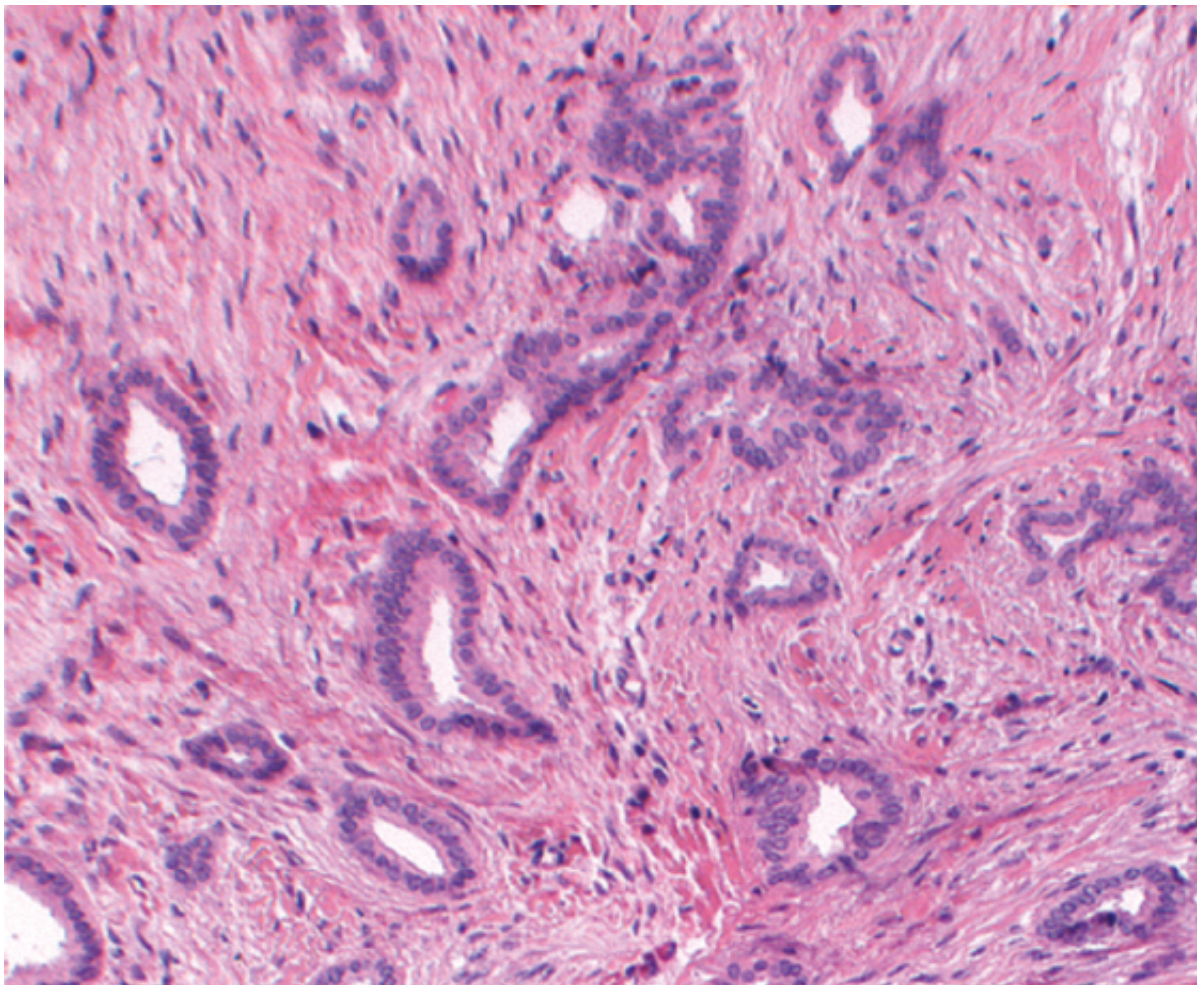


consist of sheets or large anaplastic cells that packing, non-circumscribed lesions they can be mistaken for fibroadenomas. There is invariably a pronounced lymphocytic infiltrate, which is usually absent or minimal. Medullary carcinomas, or medullary-like carcinomas, are more frequent in women with *BRCA1* mutations, although most women with medullary carcinomas are not carriers. These carcinomas uniformly lack hormone receptors and do not overexpress HER2/NEU.

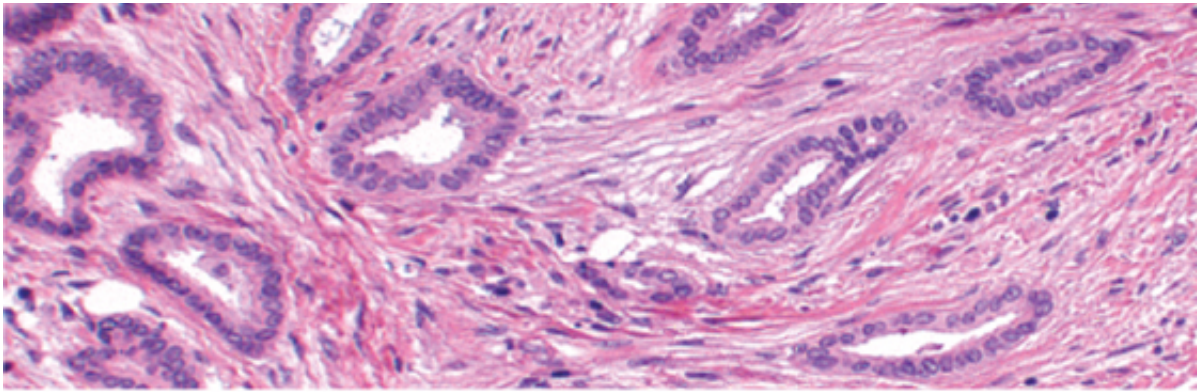
**Colloid (mucinous) carcinoma** is also a rare subtype. The tumor cells produce abundant extracellular mucin that dissects into the surrounding stroma (Fig. 19-36). Like medullary carcinomas, they often present as well-circumscribed masses and can be mistaken for fibroadenomas. They are usually soft and gelatinous. Most express hormone receptors, and rare examples rarely overexpress HER2/NEU.

**Tubular carcinomas** rarely present as palpable masses but account for 10% of in situ lesions less than 1 cm found with mammographic screening. They usually present as irregular masses. Microscopically, the carcinomas consist of well-formed tubules with low-grade nuclei. Lymph node metastases are rare, and prognosis is excellent. Virtually all tubular carcinomas express hormone receptors, but overexpression of HER2/NEU is highly unusual.

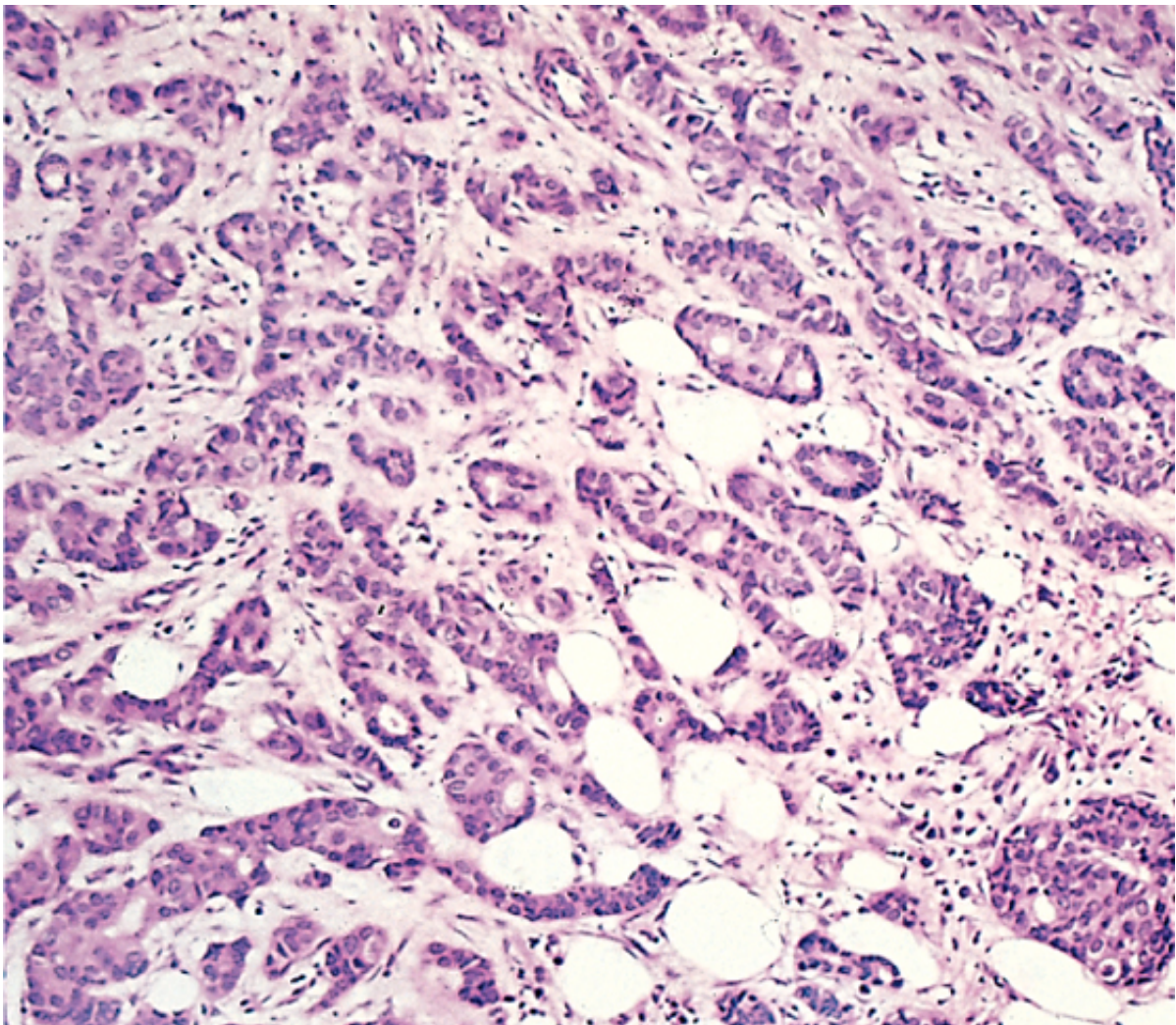
**Features Common to All Invasive Cancers.** In all the forms of breast cancer discussed, progression of the disease leads to certain local morphologic features. These include invasion of the pectoral muscles or deep fascia of the chest wall, with consequent fixation of the breast to the chest wall, as well as adherence to the overlying skin, with retraction or dimpling of the skin or nipple. The latter is an important sign, because it may be the first indication of a lesion, observed by the physician on physical examination. Involvement of the lymphatic pathways may cause localized lymphedema. Thickening of the skin becomes thickened around exaggerated hair follicles, a change known as peau d'orange.







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 Figure 19-33 Well-differentiated invasive carcinoma of no special type. Well-formed tubules and nests of cells with a surrounding desmoplastic response.



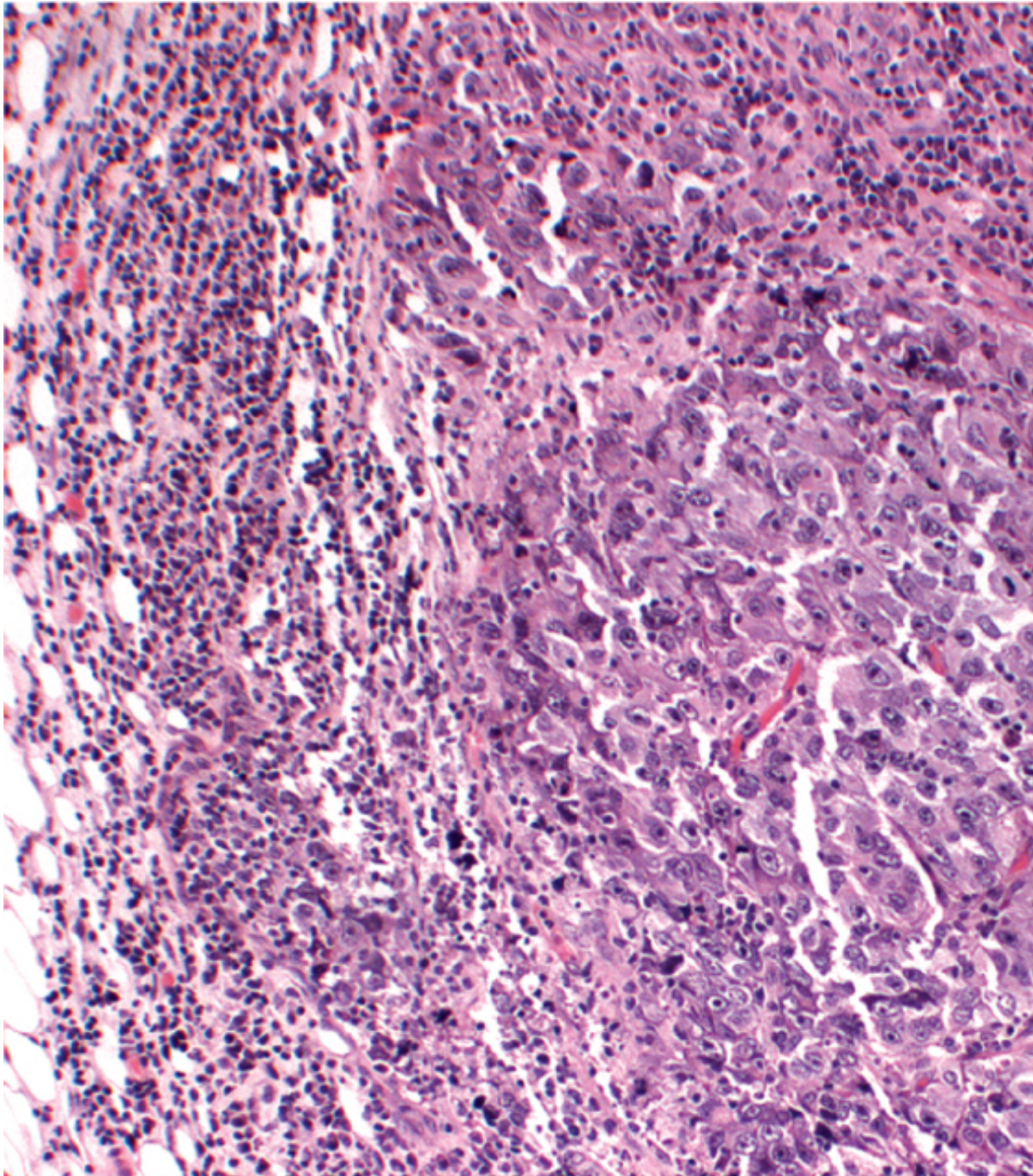
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 Figure 19-34 The margin of a cancer of the breast revealing tumorous infiltration of the adjacent tissue.

### *Spread of Breast Cancer*

Spread eventually occurs through lymphatic and hematogenous channels. Lymph node metastasis



presenting as palpable masses but in fewer than 15% of cases found by mammography. Outer quadrants typically spread first to the axillary nodes.



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Figure 19-35 Medullary carcinoma. The cells are highly pleomorphic with frequent mitoses and grow as sheets of prominent.

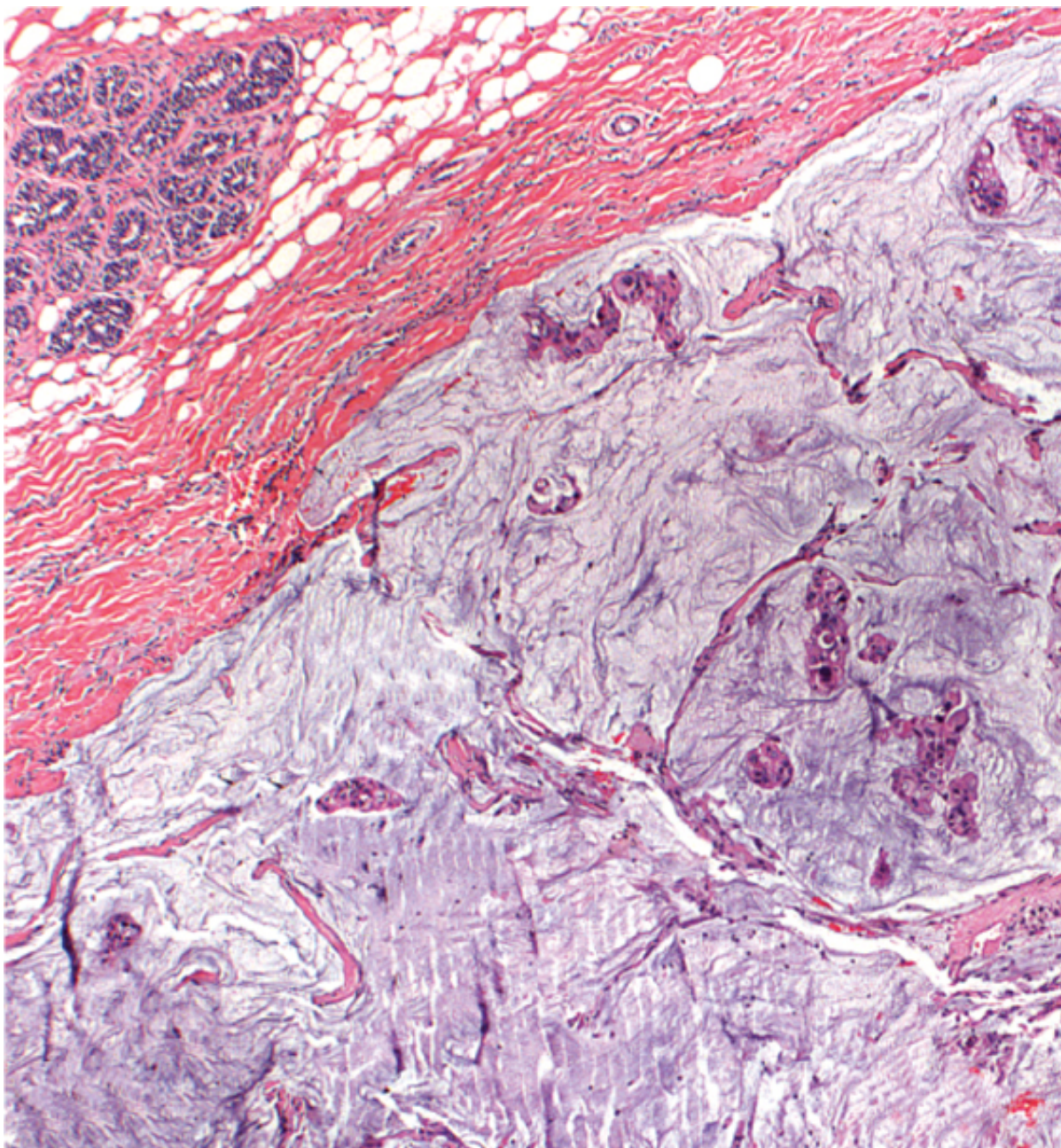
Those in the inner quadrants often involve the lymph node along the internal mammary arteries. The primary site of spread, but they may become involved only after the axillary and internal mammary dissemination eventually ensues, with metastatic involvement of almost any organ or tissue in the skeleton, liver, and adrenals and (less commonly) the brain, spleen, and pituitary. However, no site



skeleton, liver, and adrenals and (less commonly), the brain, spleen, and pituitary. However, no on  
many years after apparent therapeutic control of the primary lesion, sometimes 15 years later. Ne  
scene brightens.

### *Clinical Course*

Breast cancer is often discovered by the woman or her physician as a deceptively discrete, solitary  
time, the carcinoma is typically 2 to 3 cm in size, and involvement of the regional lymph nodes (m  
about half of patients. With mammographic screening, carcinomas are frequently detected before  
invasive carcinoma found by screening is around 1 cm in size, and only 15% of these have nodal  
DCIS is detected before the development of invasive carcinoma. As women age, fibrous breast tis  
becomes more sensitive, as a result of the increased radiolucency of the breast and the increased  
controversy over the best time to begin mammographic screening must take into account the ben  
morbidity of the majority of women who will be proved to have benign changes. Magnetic resonan  
young patients with dense breasts that are difficult to image by mammography as adjunct to mam





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Figure 19-36 Mucinous (colloid) carcinoma. The tumor cells are present as small clusters within large pools of mucin and these cancers often mimic benign masses.

Prognosis is influenced by the following variables (note that the first three are components of tumor staging):

1. *The size of the primary carcinoma.* Invasive carcinomas smaller than 1 cm have an excellent prognosis and may not require systemic therapy.
2. *Lymph node involvement and the number of lymph nodes involved by metastases.* With no lymph node involvement, the 5-year survival rate is close to 90%. The survival rate decreases with each involved lymph node. Sentinel node biopsy has been introduced as an alternative, less morbid, procedure. The first one or two draining lymph nodes are identified by using a dye or a radiotracer. If the sentinel lymph node is highly predictive of the absence of metastatic carcinoma in the remaining nodes, the rest of the nodes can be examined by more extensive procedures, such as serial sectioning or immunohistochemistry for positive cells. However, the clinical significance of the finding of micrometastases (defined as clusters of tumor cells less than 0.2 cm) is still unknown.
3. *Distant metastases.* Patients who develop hematogenous spread are rarely curable, although some may respond to systemic therapy.
4. *The grade of the carcinoma.* The most common grading system for breast cancer evaluates nuclear atypia and mitotic rate to divide carcinomas into three groups. Well-differentiated carcinomas have a survival rate that approaches that of poorly differentiated carcinomas. Moderately differentiated carcinomas initially have a survival rate that approaches that of poorly differentiated carcinomas.
5. *The histologic type of carcinoma.* All specialized types of breast carcinoma (tubular, medullary, mucinous) have a somewhat better prognosis than carcinomas of no special type ("ductal carcinoma in situ").
6. *The presence or absence of estrogen or progesterone receptors.* The presence of hormone receptors is a good prognostic factor. However, the reason for determining their presence is to predict the response to anti-hormone therapy. About 80% of breast carcinomas respond to anti-estrogen therapy (oophorectomy or tamoxifen) is seen in women whose tumors have estrogen receptors. Lower rates of response (25% to 45%) are seen if only one of the receptors is present. Very few patients (<10%) respond.
7. *The proliferative rate of the cancer.* Proliferation can be measured by mitotic counts, flow cytometry, or markers for cell cycle proteins. Mitotic counts are included as part of the grading system. Tumors with high proliferative rates are associated with a poorer prognosis. High proliferative rates have not been determined. High proliferative rates are associated with a poorer prognosis.
8. *Aneuploidy.* Carcinomas with an abnormal DNA content (aneuploidy) have a slightly worse prognosis than those with a DNA content similar to normal cells.
9. *Overexpression of HER2/NEU.* Overexpression of this membrane-bound protein is almost always associated with a poor prognosis. Therefore, overexpression can be determined by immunohistochemistry (which detects the presence of the protein) or fluorescence in situ hybridization (which detects the number of gene copies). Overexpression of HER2/NEU is associated with a poor prognosis. However, the importance of evaluating HER2/NEU is to predict response to a monoclonal antibody therapy. This is one of the first examples whereby an antitumor antibody therapy has been developed. Overexpression of HER2/NEU is associated with a poor prognosis.

The major prognostic factors are used by the American Joint Committee on Cancer to divide breast cancer into stages as follows:

Stage 0. DCIS or LCIS (5-year survival rate: 92%). Stage I. Invasive carcinoma 2 cm or less in diameter (without nodal involvement) or only metastases < 0.02 cm in diameter (5-year survival rate: 92%). Stage II. Invasive carcinoma 5 cm or less in diameter with up to three involved axillary nodes or invasive carcinoma with nodal involvement (5-year survival rate: 75%). Stage III. Invasive carcinoma 5 cm or less in diameter with up to three involved axillary nodes; invasive carcinoma greater than 5 cm in diameter with nodal involvement; or invasive carcinoma with involvement of the ipsilateral internal mammary lymph nodes (5-year survival rate: 55%). Stage IV. Invasive carcinoma with skin involvement (edema, ulceration, or satellite skin nodules), chest wall fixation, or distant metastases (5-year survival rate: 46%). Stage IV. Any breast cancer with distant metastases (5-year survival rate: 46%).







## MALE BREAST

The rudimentary male breast is relatively free of pathologic involvement. Only two disorders occur with sufficient frequency to be considered here: *gynecomastia* and *carcinoma*.

### Gynecomastia

As in females, male breasts are subject to hormonal influences, but they are considerably less sensitive than are female breasts. Nonetheless, enlargement of the male breast, or gynecomastia, may occur in response to absolute or relative estrogen excesses.

Gynecomastia, then, is the male analogue of fibrocystic change in the female. The most important cause of such hyperestrogenism in the male is cirrhosis of the liver, with consequent inability of the liver to metabolize estrogens. Other causes include Klinefelter syndrome, estrogen-secreting tumors, estrogen therapy, and, occasionally, digitalis therapy. Physiologic gynecomastia often occurs in puberty and in extreme old age.

The morphologic features of gynecomastia are similar to those of intraductal hyperplasia. Grossly, a button-like, subareolar swelling develops, usually in both breasts but occasionally in only one.

### Carcinoma

This is a rare occurrence, with a frequency ratio to breast cancer in the female of 1 : 125. It occurs in advanced age. Because of the scant amount of breast substance in the male, the tumor rapidly infiltrates the overlying skin and underlying thoracic wall. Both morphologically and biologically, these tumors resemble invasive carcinomas in the female. Unfortunately, almost half have spread to regional nodes and more distant sites by the time they are discovered.

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## 20 The Endocrine System

ANIRBAN MAITRA MBBS

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The endocrine system contains a highly integrated and widely distributed group of organs that orchestrates a state of metabolic equilibrium, or homeostasis, between the various tissues of the body. Signaling by extracellular secreted molecules can be classified into three types: autocrine, paracrine, or endocrine, based on the distance over which the signal acts ([Chapter 3](#)). In endocrine signaling, the secreted molecules, which are frequently called *hormones*, act on target cells distant from their site of synthesis. An endocrine hormone is frequently carried by the blood from its site of release to its target. Increased activity of the target tissue often down-regulates the activity of the gland that secretes the stimulating hormone, a process known as *feedback inhibition*.

Hormones can be classified into several broad categories, based on the nature of their receptors:

*Hormones that trigger biochemical signals upon interacting with cell-surface receptors:*

This large class of compounds is composed of two groups: (1) peptide hormones, such as *growth hormone* and *insulin*, and (2) small molecules, such as *epinephrine*<sup>Rx</sup>.

Binding of these hormones to cell surface receptors leads to an increase in intracellular signaling molecules, termed *second messengers*, such as cyclic *adenosine*<sup>Rx</sup> monophosphate (cAMP); production of mediators from membrane phospholipids (e.g., inositol 1,4,5-trisphosphate); and shifts in the intracellular levels of ionized calcium. The elevated levels of one or more of these can control proliferation, differentiation, survival, and functional activity of cells, mainly by regulating the expression of specific genes.

*Hormones that diffuse across the plasma membrane and interact with intracellular receptors:* Many lipid-soluble hormones diffuse across the plasma membrane and interact with receptors in the cytosol or the nucleus. The resulting hormone-receptor complexes bind specifically to promoter and enhancer elements in DNA, thereby affecting the expression of specific target genes. Hormones of this type include the *steroids* (e.g., estrogen, *progesterone*<sup>Rx</sup>, and glucocorticoids) and *thyroxine*.

Several processes may disturb the normal activity of the endocrine system, including impaired synthesis or release of hormones, abnormal interactions between hormones and their target tissues, and abnormal responses of target organs to their hormones. Endocrine diseases can be generally classified as (1) diseases of *underproduction or overproduction* of hormones and their resulting biochemical and clinical consequences, and (2) diseases associated with the development of *mass lesions*, which may be nonfunctional or may be associated with overproduction or underproduction of hormones. The study of endocrine diseases requires integration of morphologic findings with biochemical measurements of the levels of hormones, their regulators, and other metabolites.







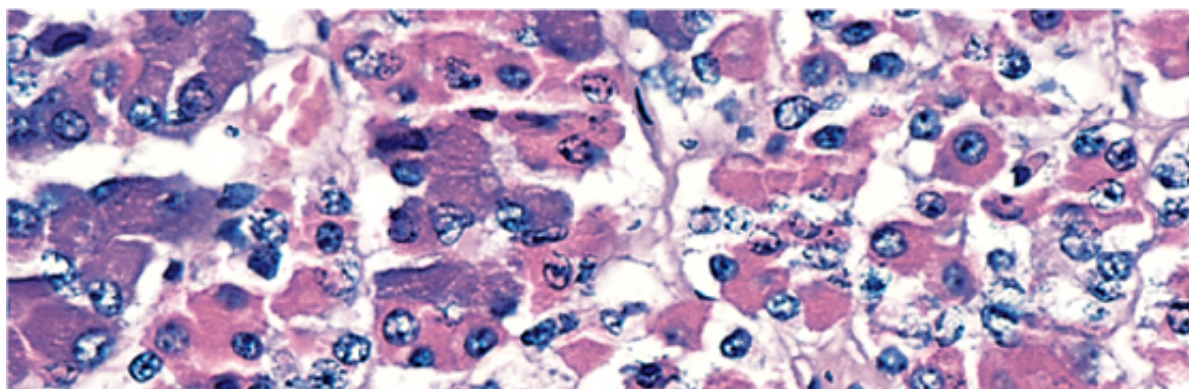
## PITUITARY

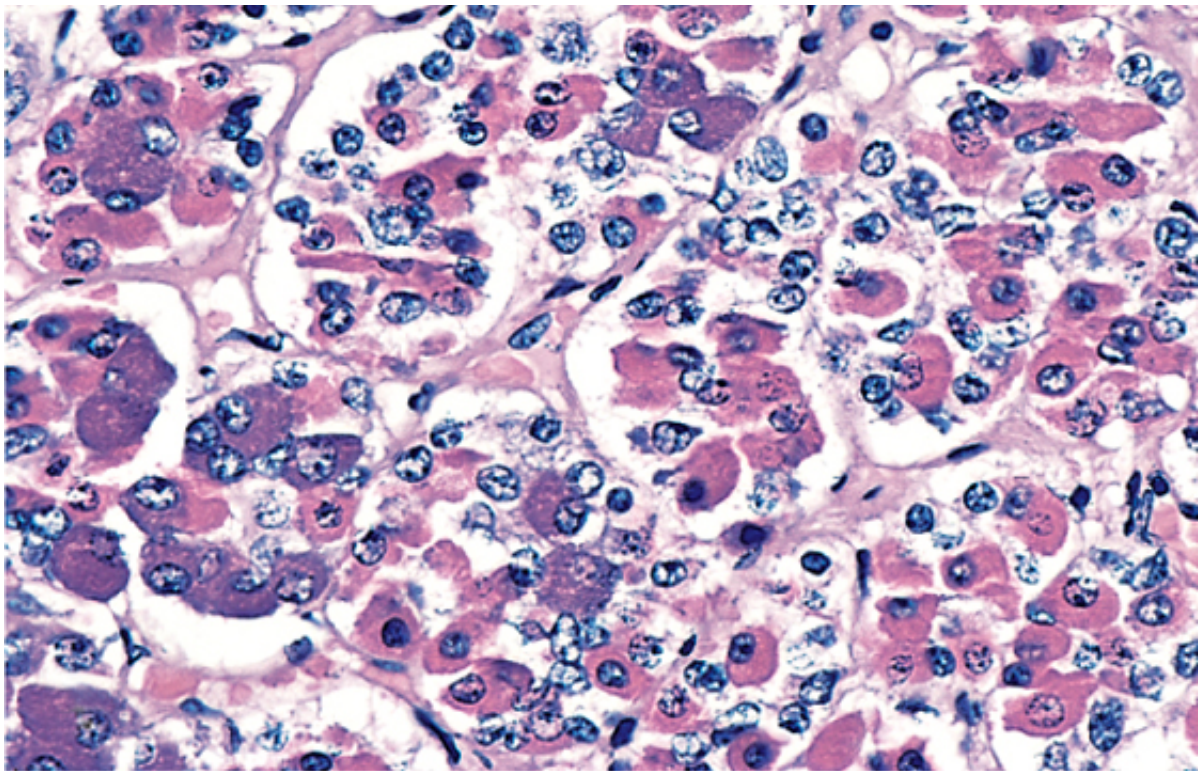
The pituitary gland is a small, bean-shaped structure that lies at the base of the brain within the sella turcica, related to the hypothalamus, with which it is connected by both a "stalk," composed of axons extending from the hypothalamus, and a primary capillary venous plexus constituting a portal circulation. Along with the hypothalamus, the pituitary has a close relationship with other endocrine glands. The pituitary is composed of two morphologically and functionally distinct parts: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). Diseases of the pituitary, according to their location, affect the anterior lobe and those that primarily affect the posterior lobe.

The *anterior pituitary*, or *adenohypophysis*, is composed of epithelial cells derived embryologically from the oral ectoderm. In routine histologic sections, a colorful array of cells containing basophilic cytoplasm, eosinophilic cytoplasm, or ("chromophobic") cytoplasm is present (Fig. 20-1). Detailed studies using electron microscopy and immunohistochemistry have demonstrated that the staining properties of these cells are related to the presence of various trophic hormones. Some cells release trophic hormones in turn under the control of factors produced in the hypothalamus; others stimulate and promote pituitary hormone release, others (e.g., somatostatin and dopamine) are inhibitory. Rarely, symptoms of pituitary disease may be caused by an excess or lack of the hypothalamic factors.

Symptoms of pituitary disease can be divided into the following:

**Hyperpituitarism:** This disorder arises from excessive secretion of trophic hormones. It most commonly is caused by an *adenoma*, but may also be caused by other pituitary and extra-pituitary lesions that are described later in this chapter. **Hypopituitarism:** This disorder is characterized by a deficiency of trophic hormones and results from a variety of destructive processes, including *ischemic infarction*, *inflammatory reactions*. In addition, *nonfunctional pituitary adenomas* may encroach upon the normal pituitary parenchyma and cause hypopituitarism. **Local mass effects:** Among the earliest changes are the *radiographic abnormalities of the sella turcica*, including sellar expansion, bony erosion, and enlargement of the sella. Because of the close proximity of the optic nerves and chiasm to the sella, expanding pituitary tumors may compress the optic chiasm, resulting in *visual field abnormalities*, classically in the form of *bitemporal hemianopsia*. In addition, a variety of other visual field abnormalities may occur. As in the case of any expanding intracranial mass, pituitary adenomas may cause *elevated intracranial pressure*, including headache, nausea, and vomiting. Pituitary adenomas that extend into the base of the brain (invasive pituitary adenoma) produce *seizures* or *obstructive hydrocephalus*. Pituitary adenomas can result in *cranial nerve palsy*. On occasion, acute hemorrhage into an adenoma is associated with enlargement of the lesion and depression of consciousness, a situation appropriately termed *apoplexy* is a neurosurgical emergency, because it may cause sudden death.





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 Figure 20-1 Photomicrograph of normal anterior pituitary. The gland is populated by several distinct cell populations that produce different hormones. Each of the hormones has different staining characteristics, resulting in a mixture of cell types.

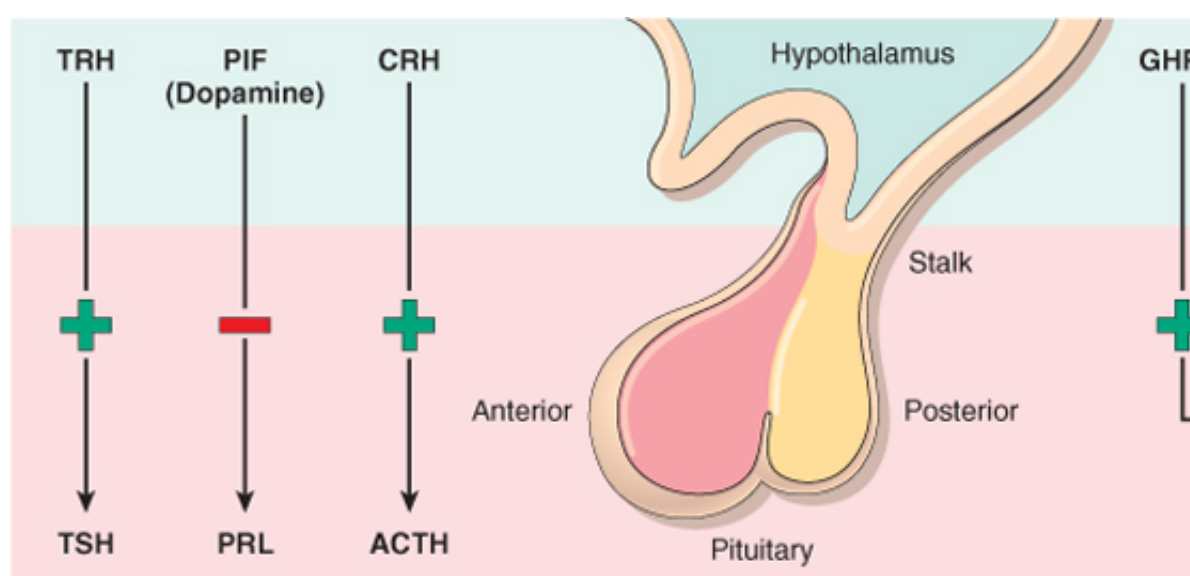


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## HYPERPITUITARISM AND PITUITARY ADENOMAS

The most common cause of hyperpituitarism is an adenoma arising in the anterior lobe. Other, less common causes include carcinomas of the anterior pituitary, secretion of hormones by some extra-pituitary tumors, and pituitary adenomas. Pituitary adenomas are classified on the basis of hormone(s) produced by the neoplastic cells, which is determined by immunohistochemical and/or ultrastructural examination of the neoplastic cell. Pituitary adenomas can be functional (i.e., associated with hormone excess) or nonfunctional (i.e., immunohistochemical and/or ultrastructural demonstration of hormone production at the site of the tumor without clinical manifestations of hormone excess). Both functional and nonfunctional pituitary adenomas are usually composed of a single predominant hormone, although exceptions are known to occur. Some pituitary adenomas produce growth hormone and prolactin being the most common combination; rarely, pituitary adenomas are plurihormonal. Pituitary adenomas can be hormone negative, based on absence of immunohistochemical reactivity and ultrastructural differentiation.



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Figure 20-2 The adenohypophysis (anterior pituitary) releases six hormones that are, in turn, under the control of releasing factors: ACTH, adrenocorticotropic hormone (corticotropin<sub>R</sub>); FSH, follicle-stimulating hormone; GH, growth hormone; PRL, prolactin; and TSH, thyroid-stimulating hormone (thyrotropin<sub>R</sub>). The stimulatory releasing factors are growth hormone-releasing hormone (GHRH), GnRH (gonadotropin-releasing hormone), and TRH (thyrotropin-releasing hormone). The inhibitory releasing factors are growth hormone-inhibitory hormone (GIH, or somatostatin) and PIF (prolactin-inhibitory factor).

**Table 20-1. Classification of Pituitary Adenomas\***

Prolactin cell (lactotroph) adenoma
Growth hormone cell (somatotroph) adenoma
Thyroid-stimulating hormone cell (thyrotroph) adenomas
ACTH cell (corticotroph) adenomas
Gonadotroph cell adenomas
Silent gonadotroph adenomas includes most so-called null cell adenomas
Mixed (plurihormonal) adenomas
Growth hormone-prolactin mixed adenomas most common



## Hormone-negative adenomas

\*For each of the pituitary cell types, the adenoma may be *functional* (producing symptoms of hormone excess) or *silent*. The hetero includes silent pituitary adenomas and true hormone-negative adenomas (rare).  
ACTH, adrenocorticotrophic hormone.

Most pituitary adenomas occur as isolated lesions. In about 3% of cases, however, adenomas are *neoplasia type 1* (MEN-1, discussed later). Pituitary adenomas are designated, somewhat arbitrarily, as *microadenomas* if they are less than 1 cm in diameter and *macroadenomas* if they exceed 1 cm in diameter. Silent and hormone-negative adenomas are often discovered at a later stage than those associated with endocrine abnormalities and are therefore more clinically significant. In addition, these adenomas may cause *hypopituitarism* as they encroach on and destroy adjacent normal pituitary tissue.

### Pathogenesis

There have been several advances in understanding the molecular pathogenesis of pituitary adenomas. G-protein (G-protein) mutations are the best-characterized molecular abnormalities in these neoplasms. In signal transduction, transmitting signals from *cell surface receptors* (e.g., growth hormone-releasing hormone receptor), which then generate *second messengers* (e.g., cAMP). G-protein: receptors following ligand binding, and are linked to the receptors by various adaptors.  $G_s$  is a stimulatory G-protein in signal transduction in several endocrine organs, including the pituitary. The  $\alpha$ -subunit of  $G_s$  ( $G_{s\alpha}$ ) is located on chromosome 20q13. In the basal state,  $G_s$  exists as an inactive protein, with GDP bound to the  $\alpha$ -subunit of  $G_{s\alpha}$ . Upon interaction with the ligand-bound cell surface receptor, GDP dissociates and GTP binds to the  $\alpha$ -subunit. GTP-bound  $G_{s\alpha}$  directly interacts with and activates its effectors (such as adenylyl cyclase), with which cAMP acts as a potent mitogenic stimulus for a variety of endocrine cell types, promoting cellular proliferation and secretion. The activation of  $G_{s\alpha}$ , and the resultant generation of cAMP, are *transient* because of the  $\beta\gamma$ -subunit, which hydrolyzes GTP into GDP. A *mutation in the  $\alpha$ -subunit that interferes with its intrinsic GTPase activity* results in *constitutive activation of  $G_{s\alpha}$ , persistent generation of cAMP, and unchecked cellular proliferation*. This is the case in secreting somatotroph cell adenomas and a minority of adrenocorticotrophic hormone (ACTH)-secreting adenomas, which harbor *GNAS1* mutations. Pituitary adenomas that arise in the context of familial MEN-1 syndrome harbor mutations in the *menin* gene (discussed later). Additional molecular abnormalities present in *aggressive or advanced* adenomas include mutations of the *RAS* oncogene, overexpression of the *C-MYC* oncogene, and inactivation of the *p53* tumor suppressor gene, suggesting that these genetic events are linked to disease progression.

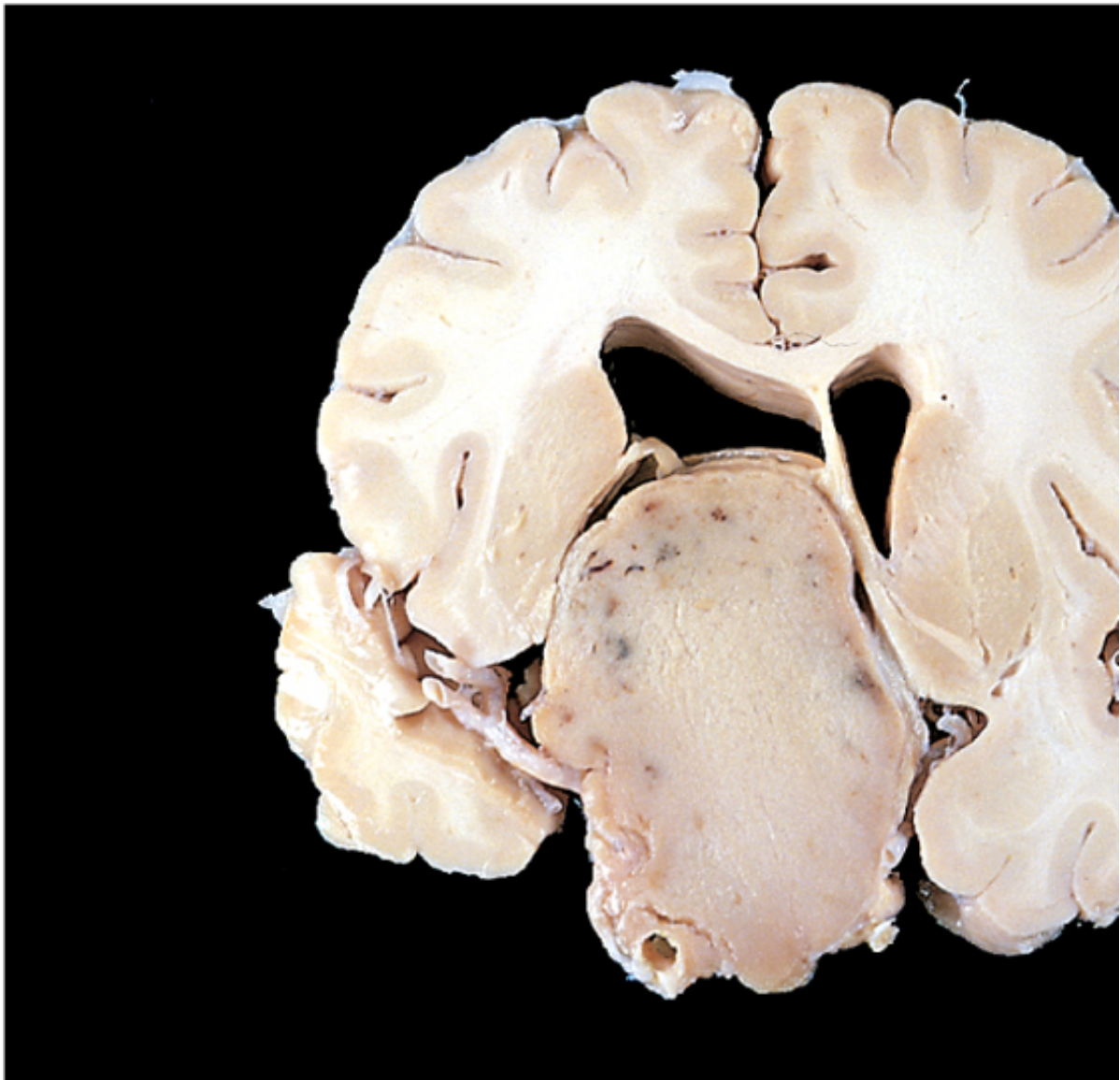
### Morphology

The usual pituitary adenoma is a well-circumscribed, soft lesion that may, in the early stages, be confined by the sella turcica. Larger lesions typically extend superiorly through the suprasellar region, where they often compress the optic chiasm and adjacent structures. As adenomas expand, they frequently erode the sella turcica and anterior clinoid process. In as many as 30% of cases, adenomas extend locally into the cavernous and sphenoidal sinuses. In as many as 30% of cases, adenomas are grossly nonencapsulated and infiltrate adjacent bone, dura, and (uncommonly) brain tissue. These are designated **invasive adenomas**. Foci of hemorrhage and/or necrosis are common in larger lesions.

Microscopically, pituitary adenomas are composed of relatively uniform, polygonal cells arranged in cords, or papillae. Supporting connective tissue, or reticulin, is sparse, accounting for the histologic consistency of many lesions. The nuclei of the neoplastic cells may be uniform or pleomorphic, but are usually scanty. The cytoplasm of the constituent cells may be acidophilic, basophilic, or amphophilic, depending on the type and amount of secretory product within the cell, but it is fairly uniform within a neoplasm. **This cellular monomorphism and the absence of a significant reticulin reaction are characteristic of pituitary adenomas from non-neoplastic anterior pituitary parenchyma** (Fig. 2). The site of origin of the adenoma cannot be reliably predicted from its histologic appearance.

Clinically diagnosed pituitary adenomas are responsible for about 10% of intracranial neoplasms. In fact, many as 25% of routine autopsies. In fact, the most recent data using high-resolution computed tomography and magnetic resonance imaging suggest that approximately 20% of "normal" adult pituitary glands harbor an incidental lesion, usually a silent adenoma. Pituitary adenomas are usually found in adults, with a peak incidence between 40 and 60 years of age.

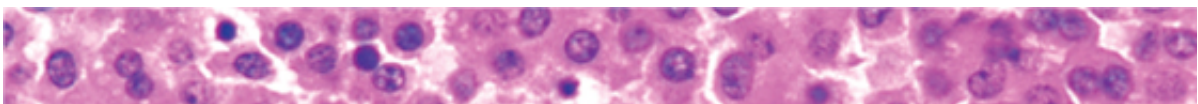


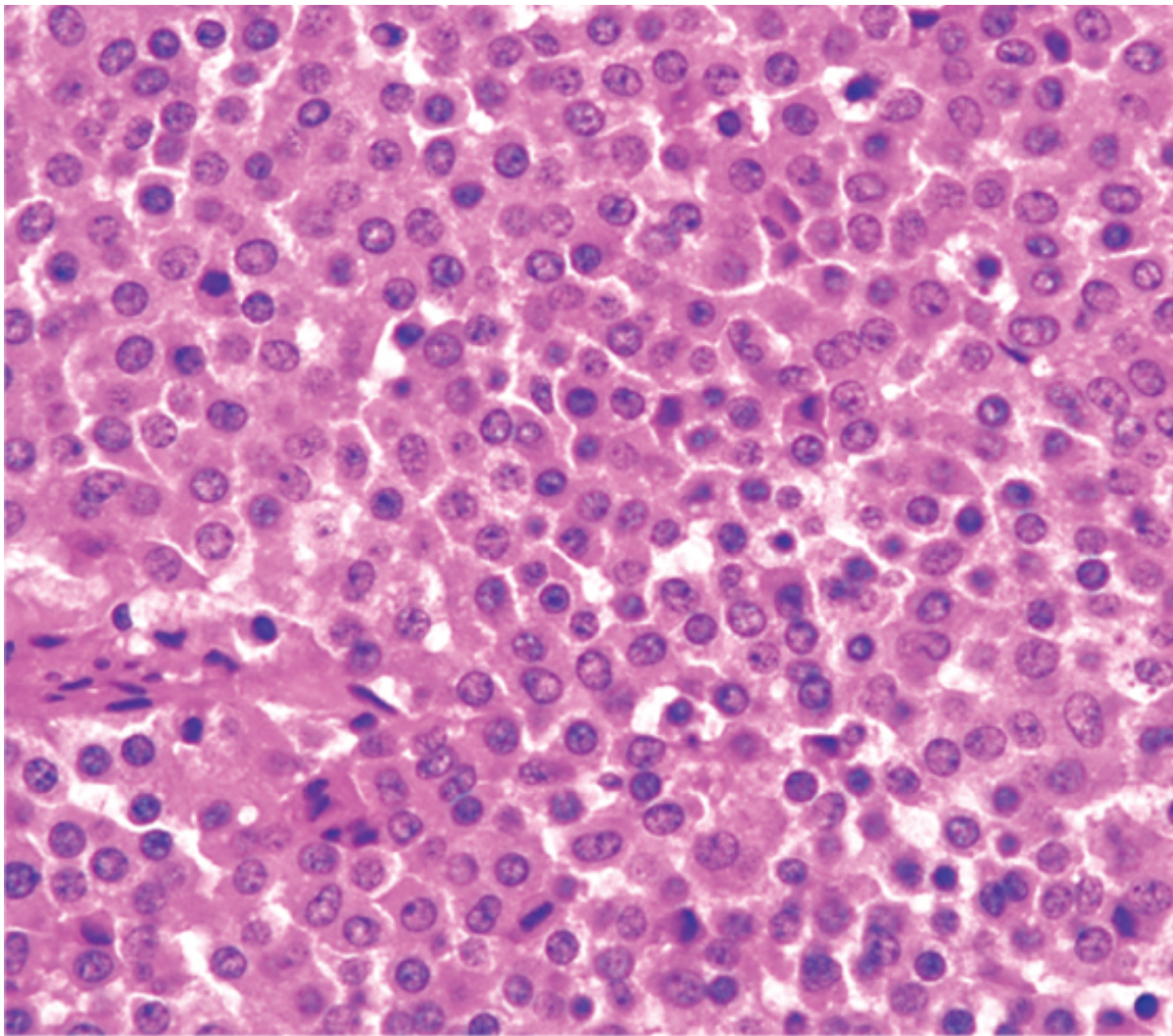


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Figure 20-3 Gross view of a pituitary adenoma. This massive, nonfunctional adenoma has grown far beyond the c  
overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those

## SUMMARY

**Hyperpituitarism** The most common cause of hyperpituitarism is an anterior pituitary adenoma. Pituitary adenomas can be macroadenomas (>1 cm) or microadenomas (<1 cm). Clinically, they can be functional or nonfunctional. Most adenomas consist of one cell type that secretes a single hormone, although there are exceptions. Mutation of the *GNAS1* gene, which encodes for a stimulatory G-protein, is one of the more common genetic alterations. Distinctive morphologic features of most adenomas are their cellular monomorphism and the presence of a well-developed reticulin network.





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Figure 20-4 Photomicrograph of pituitary adenoma. The monomorphism of these cells contrasts markedly to the mixture of cell types seen in Figure 20-1. Note also the absence of reticulin network.

### Prolactinomas

Prolactinomas are the most common type of hyperfunctioning pituitary adenoma. They range from small, nonexpansile tumors associated with considerable mass effect. Prolactin is demonstrable within the cytoplasm using immunohistochemical techniques.

*Hyperprolactinemia* causes amenorrhea, galactorrhea, loss of libido, and infertility. Because many manifestations of hyperprolactinemia (e.g., amenorrhea) are more obvious in premenopausal females than in males, prolactinomas are usually diagnosed at an earlier stage in females of reproductive age than in males. In males, manifestations may be quite subtle in men and older women, in whom the tumors may reach considerable size before coming to attention. Hyperprolactinemia may be caused by conditions other than prolactin-secreting pituitary adenoma, including exogenous dose estrogen therapy, renal failure, hypothyroidism, hypothalamic lesions, and dopamine-inhibiting drugs. Any mass in the suprasellar compartment may disturb the normal inhibitory influence of hypothalamic dopamine on prolactin secretion, known as the *stalk effect*. It should be kept in mind, therefore, that *mild* elevation of prolactin in an individual with a pituitary adenoma do not necessarily indicate a prolactin-secreting neoplasm.

### Growth Hormone-Producing Adenomas

Growth hormone-producing (somatotroph cell) neoplasms, including those that produce a mixture of growth hormone and prolactin, are the second most common type of functional pituitary adenoma. Because the

(e.g., prolactin), are the second most common type of functional pituitary adenoma. Because the effect of growth hormone may be subtle, somatotroph cell adenomas may be quite large by the time they are clinically apparent. Growth hormone-producing adenomas are composed of densely or sparsely granulated cells, and demonstrate growth hormone within the cytoplasm of the neoplastic cells. Small amounts of immunoreactive growth hormone may be detected in the serum of patients with these tumors.

Persistent hypersecretion of growth hormone stimulates the hepatic secretion of insulin-like growth factor-1 (IGF-1), which is responsible for many of the clinical manifestations. If a growth hormone-secreting adenoma occurs before the epiphyseal plates are closed in prepubertal children, excessive levels of growth hormone result in *gigantism*. This is characterized by disproportionately long arms and legs. If elevated levels of growth hormone persist, or persist in adults, individuals develop *acromegaly*, in which growth is most conspicuous in soft tissues, skin, and visceroskeletal structures. Enlargement of the jaw results in its protrusion (prognathism), with broadening of the lower jaw. The hands and feet are enlarged, with broad, sausage-like fingers. In practice, most cases of gigantism or acromegaly. Growth hormone excess is also associated with a number of other disturbances, including diabetes mellitus, generalized muscle weakness, hypertension, arthritis, osteoporosis, and congestive heart failure. These signs and symptoms are demonstrable in a number of growth hormone-producing adenomas and in some cases may be the only signs and symptoms of hyperprolactinemia.

### Corticotroph Cell Adenomas

Most corticotroph cell adenomas are small (microadenomas) at the time of diagnosis, although some may be larger. Corticotroph adenomas stain positively with periodic acid-Schiff (PAS) stains, as a result of the accumulation of glycogen. In the case of other pituitary hormones, the secretory granules can be detected by immunohistochemical staining. Corticotroph adenomas appear as membrane-bound, electron-dense granules averaging 300 nm in diameter.

Corticotroph cell adenomas may be clinically silent or may cause *hypercortisolism* (also known as Cushing's syndrome) because of the stimulatory effect of ACTH on the adrenal cortex. Cushing's syndrome, discussed in more detail later, may be caused by a wide variety of conditions in addition to ACTH-producing pituitary neoplasms. In the case of excessive production of ACTH by the pituitary, the process is designated *Cushing's disease*, because it was originally described by Dr. Harvey Cushing. Large, clinically aggressive corticotroph adenomas may require surgical removal of the adrenal glands for treatment of Cushing's syndrome. This condition, known as *Nelson's syndrome*, occurs in the absence of the inhibitory effect of adrenal corticosteroids on a preexisting corticotroph microadenoma. Because of the negative feedback loop, with Nelson's syndrome, hypercortisolism does not develop. Instead, patients present with the mass effect of the tumor, because ACTH is synthesized as part of a larger prohormone that includes melanocyte-stimulating hormone (MSH), resulting in hyperpigmentation.

### Other Anterior Pituitary Neoplasms

*Gonadotroph (luteinizing hormone [LH]-producing and follicle-stimulating hormone [FSH]-producing) adenomas* are clinically recognizable because they secrete hormones inefficiently and variably, and the secretory products are not always recognizable as a clinical syndrome. Gonadotroph adenomas are most frequently found in middle-aged men. Large tumors have become large enough to cause neurologic symptoms, such as impaired vision or apoplexy. The neoplastic cells usually demonstrate immunoreactivity for the common gonadotropin  $\alpha$ -subunit and the recognition of gonadotroph-specific transcription factors has been used to identify these tumors. FSH and  $\beta$ -LH subunits; FSH is usually the predominant secreted hormone. The availability of antibodies to the gonadotropin  $\beta$ -subunit and the recognition of gonadotroph-specific transcription factors has been used to identify these tumors. Previously described hormone-negative adenomas ("null cell adenomas") as silent gonadotrophs. *Thyrotroph (thyroid-stimulating hormone [TSH]-producing) adenomas* account for about 1% of all pituitary adenomas. They are associated with hyperthyroidism. *Nonfunctioning pituitary adenomas* comprise both clinically silent counterparts of the functional adenomas described above (for example, a *silent gonadotroph adenoma*) and true *hormone-negative* adenomas. They are infrequent and, as stated above, many have been reclassified using improved diagnostic techniques. They constitute approximately 25% of all pituitary tumors. Not surprisingly, the typical presentation is mass effect. These lesions may also compromise the residual anterior pituitary sufficiently to produce hypopituitarism. *Pituitary carcinomas* are exceedingly rare. In addition to local extension beyond the sella turcica, they may metastasize.

## SUMMARY

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**Clinical Manifestations of Pituitary Adenomas**  
*Prolactinomas*: amenorrhea, low libido, and infertility  
*Growth hormone (somatotroph cell) adenomas*: gigantism (adults), impaired glucose tolerance, and diabetes mellitus  
*Corticotroph cell adenomas*: Cushing's syndrome, hyperpigmentation  
All pituitary adenomas, particularly nonfunctioning, are associated with mass effects and hypopituitarism.



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## HYPOPITUITARISM

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Hypofunction of the anterior pituitary may occur with loss or absence of 75% or more of the anterior pituitary parenchyma. This may be *congenital* (exceedingly rare) or may result from a wide range of *acquired* abnormalities that are intrinsic to the pituitary. Less frequently, disorders that interfere with the delivery of pituitary hormone-releasing factors from the hypothalamus, such as hypothalamic tumors, may also cause hypofunction of the anterior pituitary. *Hypopituitarism accompanied by evidence of posterior pituitary dysfunction in the form of diabetes insipidus (see later) is almost always of hypothalamic origin.* Most cases of anterior pituitary hypofunction are caused by the following:

Nonfunctioning pituitary adenomas (see above) Ischemic necrosis of the anterior pituitary is an important cause of pituitary insufficiency. In general, the anterior pituitary tolerates ischemic insults fairly well; loss of as much as half of the anterior pituitary parenchyma causes no clinical consequences. However, with destruction of larger amounts of the anterior pituitary ( $\geq 75\%$ ), signs and symptoms of hypopituitarism develop. *Sheehan syndrome*, or postpartum necrosis of the anterior pituitary, is the most common form of clinically significant ischemic necrosis of the anterior pituitary. During pregnancy the anterior pituitary enlarges considerably, largely because of an increase in the size and number of prolactin-secreting cells. However, this physiologic enlargement of the gland is not accompanied by an increase in blood supply from the low-pressure portal venous system. The enlarged gland is thus vulnerable to ischemic injury, especially in women who develop significant hemorrhage and hypotension during the peripartum period. The posterior pituitary, because it receives its blood directly from arterial branches, is much less susceptible to ischemic injury in this setting and is therefore usually not affected. Clinically significant pituitary necrosis may also be encountered in conditions other than pregnancy, including disseminated intravascular coagulation, sickle cell anemia, elevated intracranial pressure, traumatic injury, and shock of any origin. The residual gland is shrunken and scarred. Ablation of the pituitary by surgery or radiation Other, less common causes of anterior pituitary hypofunction include inflammatory lesions such as sarcoidosis or tuberculosis, trauma, and metastatic neoplasms involving the pituitary. Rarely, mutations affecting the pituitary transcription factor Pit-1 can cause multihormonal deficiency.

The clinical manifestations of anterior pituitary hypofunction depend on the specific hormone(s) that are lacking. Children can develop growth failure (*pituitary dwarfism*) as a result of growth hormone deficiency. Gonadotropin or gonadotropin-releasing hormone (GnRH) deficiency leads to amenorrhea and infertility in women and decreased libido, impotence, and loss of pubic and axillary hair in men. TSH and ACTH deficiencies result in symptoms of hypothyroidism and hypoadrenalism, respectively, and are discussed later in the chapter. Prolactin deficiency results in failure of postpartum lactation. The anterior pituitary is also a rich source of MSH, synthesized from the same precursor molecule that produces ACTH; therefore, one of the manifestations of hypopituitarism is pallor from loss of stimulatory effects of MSH on melanocytes.



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## POSTERIOR PITUITARY SYNDROMES

The posterior pituitary, or neurohypophysis, is composed of modified glial cells (termed *pituicytes*) and axonal processes extending from nerve cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. The hypothalamic neurons produce two peptides: antidiuretic hormone (ADH) and [oxytocin<sup>®</sup>](#). They are stored in axon terminals in the neurohypophysis and released into the circulation in response to appropriate stimuli. [Oxytocin<sup>®</sup>](#) stimulates the contraction of smooth muscle in the pregnant uterus and those surrounding the lactiferous ducts of the mammary glands. Abnormal [oxytocin<sup>®</sup>](#) synthesis and release has not been associated with significant clinical abnormalities. The clinically important posterior pituitary syndromes involve ADH production. They include *diabetes insipidus* and *secretion of inappropriately high levels of ADH*.

ADH is a nonapeptide hormone synthesized predominantly in the supraoptic nucleus. In response to several different stimuli, including increased plasma oncotic pressure, left atrial distention, exercise, and certain emotional states, ADH is released from axon terminals in the neurohypophysis into the general circulation. The hormone acts on the collecting tubules of the kidney to promote the resorption of free water. ADH deficiency causes *diabetes insipidus*, a condition characterized by excessive urination (polyuria) caused by an inability of the kidney to properly resorb water from the urine. Diabetes insipidus can result from several causes, including head trauma, neoplasms, and inflammatory disorders of the hypothalamus and pituitary, and from surgical procedures involving the hypothalamus or pituitary. The condition sometimes arises spontaneously ("idiopathic") in the absence of an underlying disorder. Diabetes insipidus from ADH deficiency is designated as *central*, to differentiate it from *nephrogenic* diabetes insipidus as a result of renal tubular unresponsiveness to circulating ADH. The clinical manifestations of both diseases are similar and include the excretion of large volumes of dilute urine with an inappropriately low specific gravity. Serum sodium and osmolality are increased as a result of excessive renal loss of free water, resulting in thirst and polydipsia. Patients who can drink water can generally compensate for urinary losses; patients who are obtunded, bedridden, or otherwise limited in their ability to obtain water may develop life-threatening dehydration.

In the *syndrome of inappropriate ADH (SIADH)* secretion, ADH excess is caused by several extracranial and intracranial disorders. It causes resorption of excessive amounts of free water, with resultant hyponatremia. The most common causes of SIADH include the secretion of ectopic ADH by malignant neoplasms (particularly small-cell carcinomas of the lung), non-neoplastic diseases of the lung, and local injury to the hypothalamus and/or neurohypophysis. The clinical manifestations of SIADH are dominated by hyponatremia, cerebral edema, and resultant neurologic dysfunction. Although total body water is increased, blood volume remains normal and peripheral edema does not develop.





## THYROID

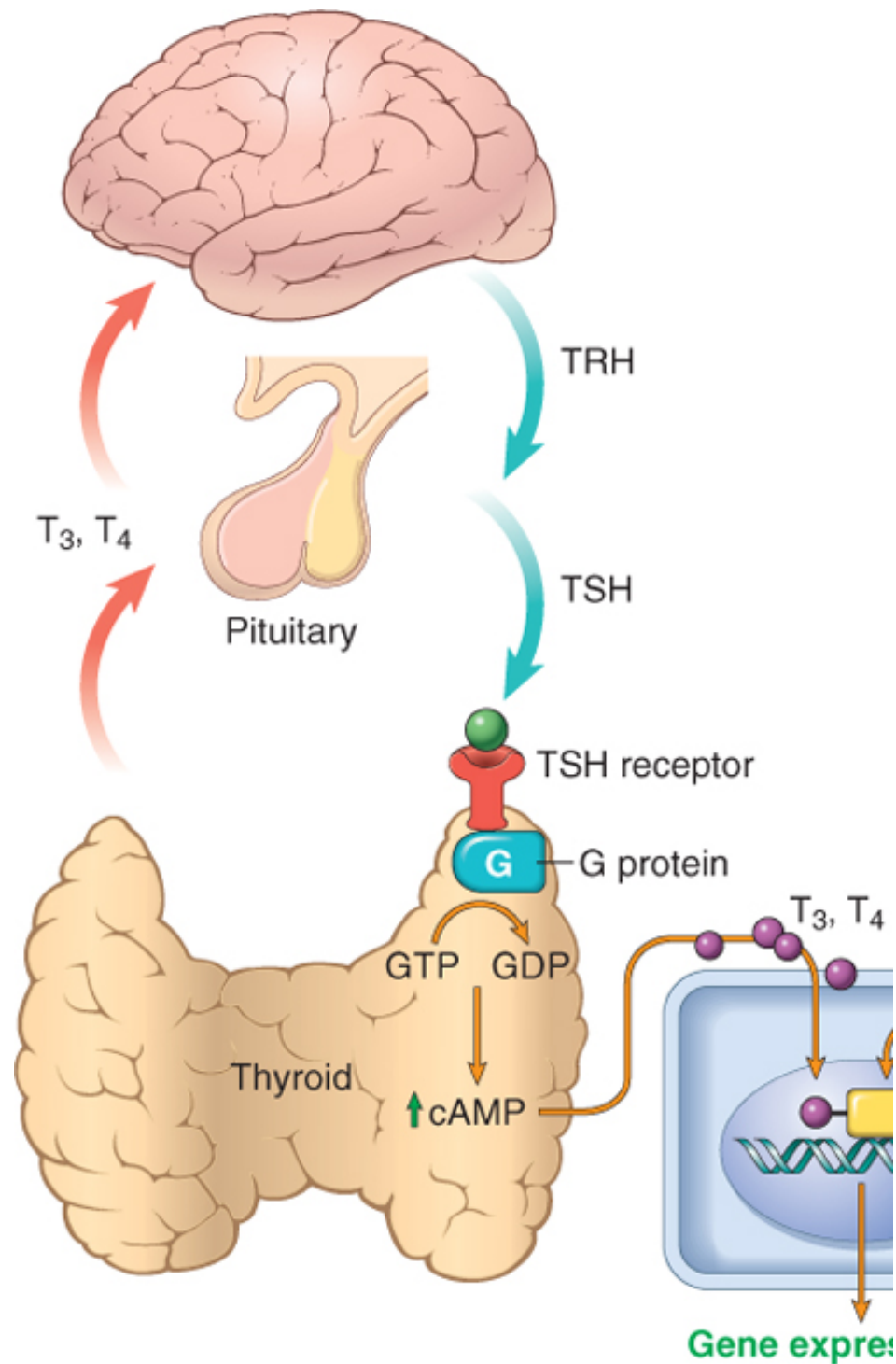
The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx. The thyroid gland develops embryologically from an evagination of the developing pharyngeal epithelium that descends from the foramen cecum at the base of the tongue to its normal position in the anterior neck. This pattern of descent explains the occasional presence of *ectopic thyroid tissue*, most commonly located at the base of the tongue (*lingual thyroid*) or at other sites abnormally high in the neck.

The thyroid is divided into lobules, each composed of about 20 to 40 evenly dispersed follicles. The follicles range from uniform to variable in size and are lined by cuboidal to low columnar epithelium, which is filled with thyroglobulin, the iodinated precursor protein of active thyroid hormone. In response to trophic factors from the hypothalamus, TSH (*thyrotropin*<sup>®</sup>) is released by thyrotrophs in the anterior pituitary into the circulation. The binding of TSH to its receptor on the thyroid follicular epithelium results in activation and conformational change in the receptor, allowing it to associate with a stimulatory G-protein (Fig. 20-5). Activation of the G-protein eventually results in an increase in intracellular cAMP levels, which stimulates thyroid hormone synthesis and release via cAMP-dependent protein kinases. Thyroid follicular epithelial cells convert thyroglobulin into *thyroxine* (T<sub>4</sub>) and lesser amounts of *triiodothyronine* (T<sub>3</sub>). T<sub>4</sub> and T<sub>3</sub> are released into the systemic circulation, where most of these peptides are reversibly bound to circulating plasma proteins, such as T<sub>4</sub>-binding globulin, for transport to peripheral tissues. The binding proteins serve to maintain the serum unbound ("free") T<sub>3</sub> and T<sub>4</sub> concentrations within narrow limits while ensuring that the hormones are readily available to the tissues. In the periphery the majority of free T<sub>4</sub> is de-iodinated to T<sub>3</sub>; the latter binds to thyroid hormone nuclear receptors in target cells with 10-fold greater affinity than T<sub>4</sub>, and has proportionately greater activity. *The interaction of thyroid hormone with its nuclear thyroid hormone receptor (TR) results in the formation of a hormone-receptor complex that binds to thyroid hormone response elements (TREs) in target genes, regulating their transcription.* Thyroid hormone has diverse cellular effects, including up-regulation of carbohydrate and lipid catabolism and stimulation of protein synthesis in a wide range of cells. The net result of these processes is an increase in the basal metabolic rate.

It is important to recognize diseases of the thyroid, because most are amenable to medical or surgical management. These diseases include conditions associated with excessive release of thyroid hormones (hyperthyroidism), those associated with thyroid hormone deficiency (hypothyroidism), and mass lesions of the thyroid. We first consider the clinical consequences of disturbed thyroid function, then focus on the disorders that generate these problems.



## HYPERTHYROIDISM



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 Figure 20-5 Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormone controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased levels of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary



releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary. Both TRH and T<sub>4</sub> levels, in turn, suppress the secretion of both TRH and TSH. This relationship is termed a *negative-feedback loop*. T<sub>3</sub> and T<sub>4</sub> levels, in turn, suppress the secretion of both TRH and TSH. This relationship is termed a *negative-feedback loop*. In the periphery, T<sub>3</sub> and T<sub>4</sub> interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex. This complex binds to so-called thyroid response elements (TREs) on target genes initiating

**Table 20-2. Cause of Thyrotoxicosis**

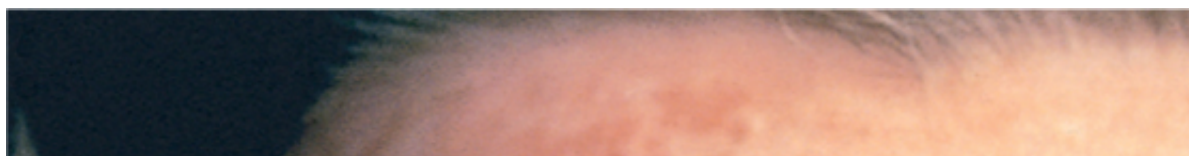
<b>Associated with Hyperthyroidism</b>
<b>PRIMARY</b>
Diffuse toxic hyperplasia (Graves disease)
Hyperfunctioning ("toxic") multinodular goiter
Hyperfunctioning ("toxic") adenoma
<b>SECONDARY</b>
TSH-secreting pituitary adenoma (rare)*
<b>Not Associated with Hyperthyroidism</b>
Subacute granulomatous thyroiditis ( <i>painful</i> )
Subacute lymphocytic thyroiditis ( <i>painless</i> )
Struma ovarii (ovarian teratoma with thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake)

\*Associated with increased TSH; all other causes of thyrotoxicosis associated with decreased TSH.  
TSH, Thyroid-stimulating hormone.

Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of free T<sub>3</sub> and T<sub>4</sub>. If the hyperfunction of the thyroid gland, it is often referred to as hyperthyroidism. However, in certain cases, such as in subacute granulomatous thyroiditis, it is due to excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extra-thyroidal source of thyroid hormone (e.g., in struma ovarii) (Table 20-2). Thus, strictly speaking, hyperthyroidism is only one (albeit the most common) cause of thyrotoxicosis. As a disclaimer, we will follow the common practice of using the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably.

The clinical manifestations of thyrotoxicosis are truly protean and include changes referable to the excessive amounts of thyroid hormone as well as those related to *overactivity of the sympathetic nervous system*.

**Constitutional symptoms:** The skin of thyrotoxic individuals tends to be soft, warm, and flushed. Sweating is common. Increased sympathetic activity and hypermetabolism result in *weight loss* and *increased appetite*. **Gastrointestinal:** Stimulation of the gut results in hypermotility, malabsorption, and tachycardia are common; elderly patients may develop congestive heart failure due to aggravated underlying heart disease. **Neuromuscular:** Patients frequently experience nervousness, tremor, and irritability. **Ocular manifestations:** A wide, staring gaze and lid lag are prominent features of thyrotoxicosis, resulting from overstimulation of the levator palpebrae superioris (Fig. 20-6). However, true *thyroid ophthalmopathy* is a feature seen only in Graves disease. **Thyroid storm** is used to designate the abrupt onset of severe thyrotoxicosis, which occurs most commonly in individuals with underlying Graves disease (discussed later), particularly in the elderly. It is characterized by extremely high catecholamine levels, as might be encountered during stress. Thyroid storm is a medical emergency; if untreated, patients die of cardiac arrhythmias. **Apathetic hyperthyroidism** refers to thyrotoxicosis in the elderly. In these individuals, age and various co-morbidities may blunt the typical features of thyroid hormone excess. The diagnosis of thyrotoxicosis in these individuals is often made during laboratory work-up for unexplained disease.





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Figure 20-6 Patient with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue causes the protuberant appearance of the eyes.

The diagnosis of hyperthyroidism is based on clinical features and laboratory data. The measurement of TSH using sensitive assays provides the most useful single screening test for hyperthyroidism, because TSH levels are decreased in the early stages, when the disease may still be subclinical. In rare cases of pituitary- or hypothalamus-associated hyperthyroidism, TSH levels are either normal or raised. A low TSH value is usually associated with increased levels of free thyroid hormone. Hyperthyroidism results predominantly from increased circulating levels of  $T_3$  ( $T_3$  toxicosis). In the majority of cases, the decreased, and direct measurement of serum  $T_3$  may be useful. Once the diagnosis of thyrotoxicosis is established, measurement of TSH and free thyroid hormone assays, measurement of radioactive iodine uptake by the thyroid gland can help determine the etiology. For example, there may be diffusely increased uptake in the whole gland (Graves disease), increased uptake in a nodule (toxic adenoma), or decreased uptake (thyroiditis).



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## HYPOTHYROIDISM

Hypothyroidism is caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone. As in the case of hyperthyroidism, this disorder is sometimes divided into primary and secondary categories, depending on whether the hypothyroidism arises from an intrinsic abnormality in the thyroid or results from hypothalamic or pituitary disease (Table 20-3).

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**Table 20-3. Causes of Hypothyroidism**

<b>Primary</b>
Postablative: surgery, radioiodine therapy, or external radiation
Hashimoto thyroiditis*
Iodine deficiency*
Congenital biosynthetic defect (dys hormonogenetic goiter)*
Drugs (lithium <sup>Rx</sup> , iodides, <i>p</i> -aminosalicylic acid)*
Rare developmental abnormalities of the thyroid (thyroid dysgenesis)
<b>Secondary</b>
Pituitary or hypothalamic failure (uncommon)

\*Associated with enlargement of thyroid ("goitrous hypothyroidism"). Hashimoto thyroiditis and postablative hypothyroidism account for the vast majority of cases of hypothyroidism, particularly in regions with adequate dietary iodine.

The clinical manifestations of hypothyroidism include cretinism and myxedema. *Cretinism* refers to hypothyroidism developing in infancy or early childhood. This disorder was formerly fairly common in areas of the world where dietary iodine deficiency is endemic, including the Himalayas, inland China, Africa, and other mountainous areas. It has now become much less frequent because of the widespread supplementation of foods with iodine. On rare occasions cretinism may also result from inborn errors in metabolism (e.g., enzyme deficiencies) that interfere with the biosynthesis of normal levels of thyroid hormone (sporadic cretinism). Clinical features of cretinism include impaired development of the skeletal system and central nervous system, with severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia. The severity of the mental impairment in cretinism seems to be directly influenced by the time at which thyroid deficiency occurs in utero. Normally, maternal hormones that are critical to fetal brain development, including T<sub>3</sub> and T<sub>4</sub>, cross the placenta. If there is maternal thyroid deficiency before the development of the fetal thyroid gland, mental retardation is severe. In contrast, reduction in maternal thyroid hormones later in pregnancy, after the fetal thyroid has developed, allows normal brain development.

Hypothyroidism developing in older children and adults results in a condition known as *myxedema*. Myxedema, or Gull disease, was first linked with thyroid dysfunction in 1873 by Sir William Gull in a paper addressing the development of a "cretinoid state" in adults. Manifestations of myxedema include generalized apathy and mental sluggishness that in the early stages of disease may mimic depression. Individuals with myxedema are listless, cold intolerant, and often obese. Mucopolysaccharide-rich edema accumulates in skin, subcutaneous tissue, and a number of visceral sites, with resultant broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice. Bowel motility is decreased, resulting in constipation. Pericardial effusions are common; in later stages the heart is enlarged. and heart failure may supervene.

Laboratory evaluation has a vital role in the diagnosis of suspected hypothyroidism because of the nonspecific nature of symptoms. *Measurement of the serum TSH is the most sensitive screening test for this disorder.* The serum TSH is increased in primary hypothyroidism because of a loss of feedback inhibition of thyrotropin-releasing hormone (TRH) and TSH production by the hypothalamus and pituitary, respectively. The TSH concentration is not increased in persons with hypothyroidism caused by primary hypothalamic or pituitary disease. Serum T<sub>4</sub> is decreased in individuals with hypothyroidism of any origin.





## THYROIDITIS

Thyroiditis, or inflammation of the thyroid gland, encompasses a diverse group of disorders characterized by inflammation. These diseases include conditions that result in acute illness with severe thyroid dysfunction (granulomatous thyroiditis) and disorders in which there is relatively little inflammation and the illness is chronic (subacute lymphocytic [painless] thyroiditis and fibrous [Reidel] thyroiditis). This section discusses three clinically significant types of thyroiditis: (1) Hashimoto thyroiditis (or chronic lymphocytic thyroiditis) and (2) subacute granulomatous thyroiditis and (3) subacute lymphocytic thyroiditis.

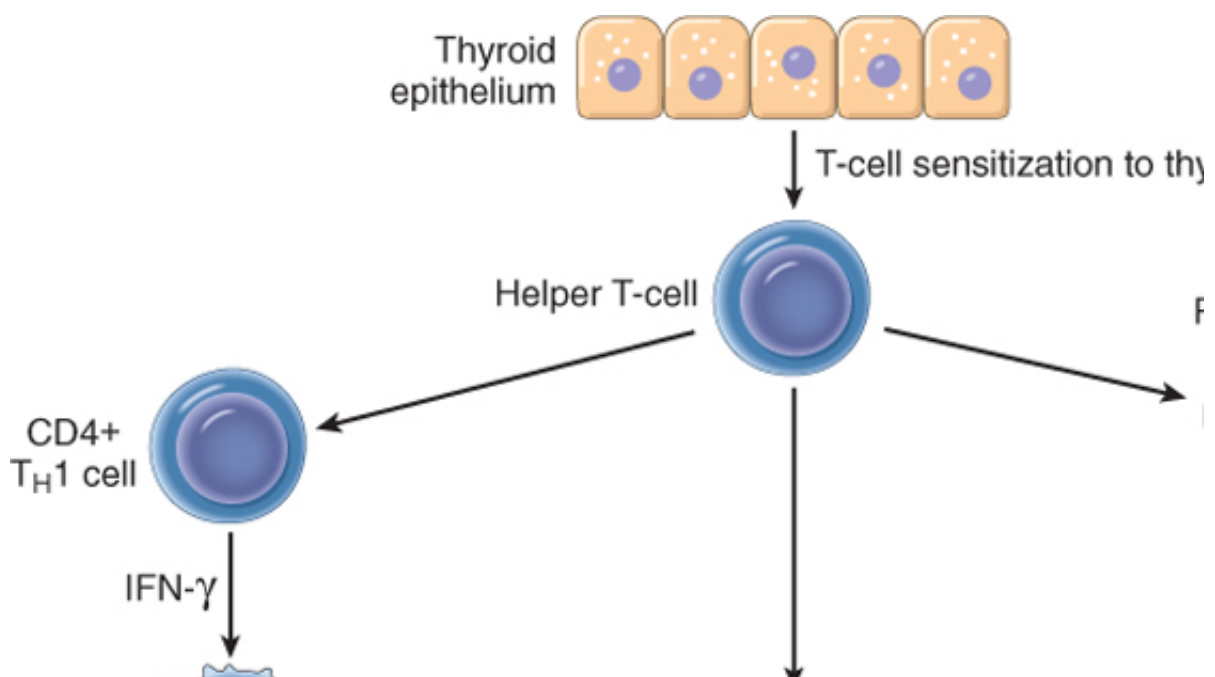
### Chronic Lymphocytic (Hashimoto) Thyroiditis

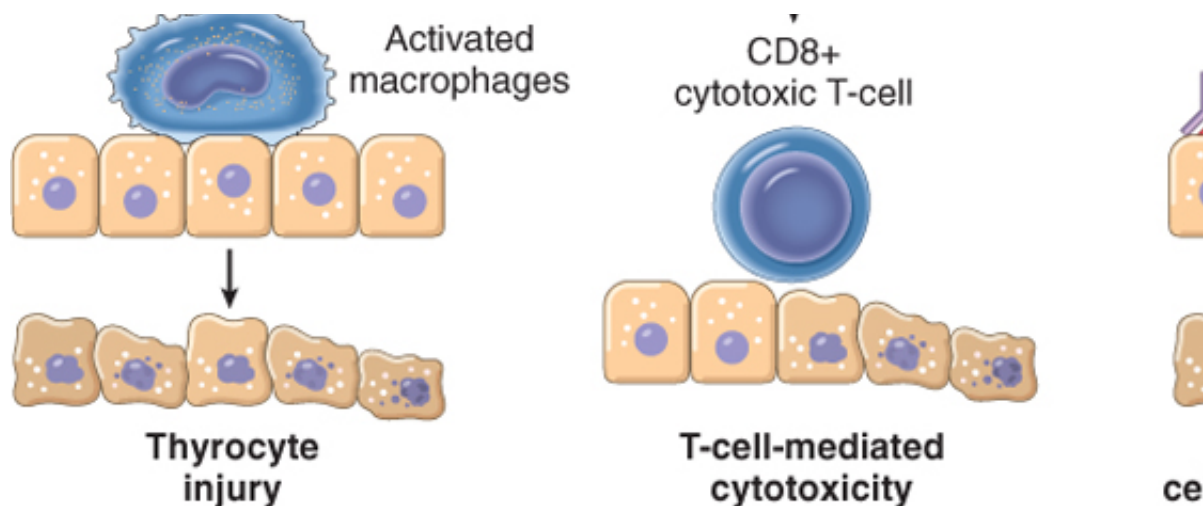
*Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine deficiency is not a problem. It is characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland. It occurs between 45 and 65 years of age and is more common in women than in men, with a female predominance. Although it is a disease of older women, it can occur in children and is a major cause of nonendemic goiter in children.*

#### Pathogenesis

Hashimoto thyroiditis is an autoimmune disease in which the overriding feature is progressive destruction of thyroid follicles (thyrocytes), which are gradually replaced by mononuclear cell infiltration and fibrosis. Multiple immunological mechanisms are involved in the death of thyrocytes (Fig. 20-7), although sensitization of autoreactive CD4<sup>+</sup> T-helper cells to thyroid antigens is the initiating event. The effector mechanisms for thyrocyte death include:

The possible reaction of CD4<sup>+</sup> T cells to thyroid antigens, thus producing cytokines—notably interleukin-2 (IL-2)—and activate macrophages, as in delayed-type hypersensitivity reactions. In addition, CD8<sup>+</sup> cytotoxic T-cell-mediated cell death: CD8<sup>+</sup> cytotoxic T cells kill these cells. Binding of antithyroid antibodies followed by antibody-dependent cellular cytotoxicity (ADCC) by natural killer (NK) cells has been invoked as another mechanism of thyrocyte death, on the basis of the presence of these cellular infiltrates. However, the importance of this mechanism is not proved.



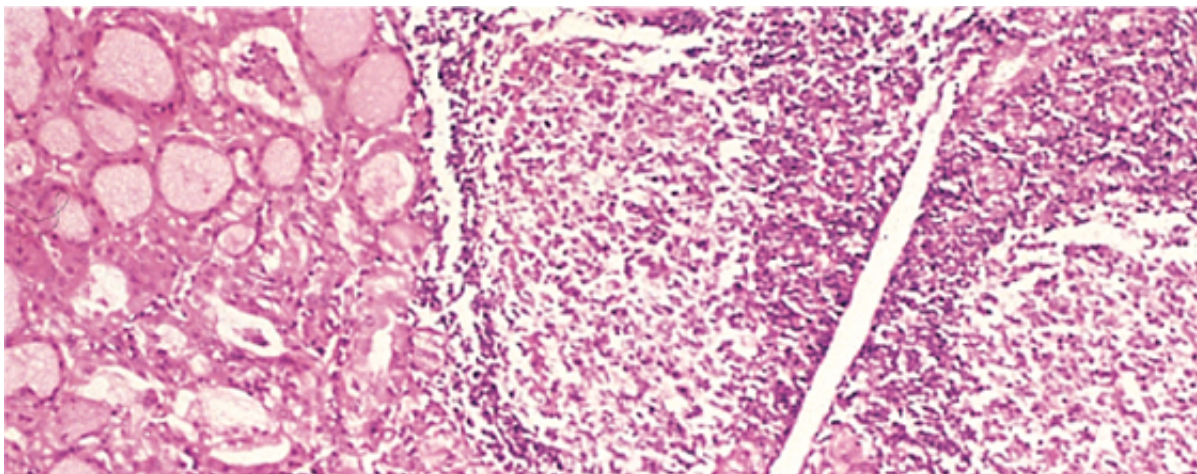


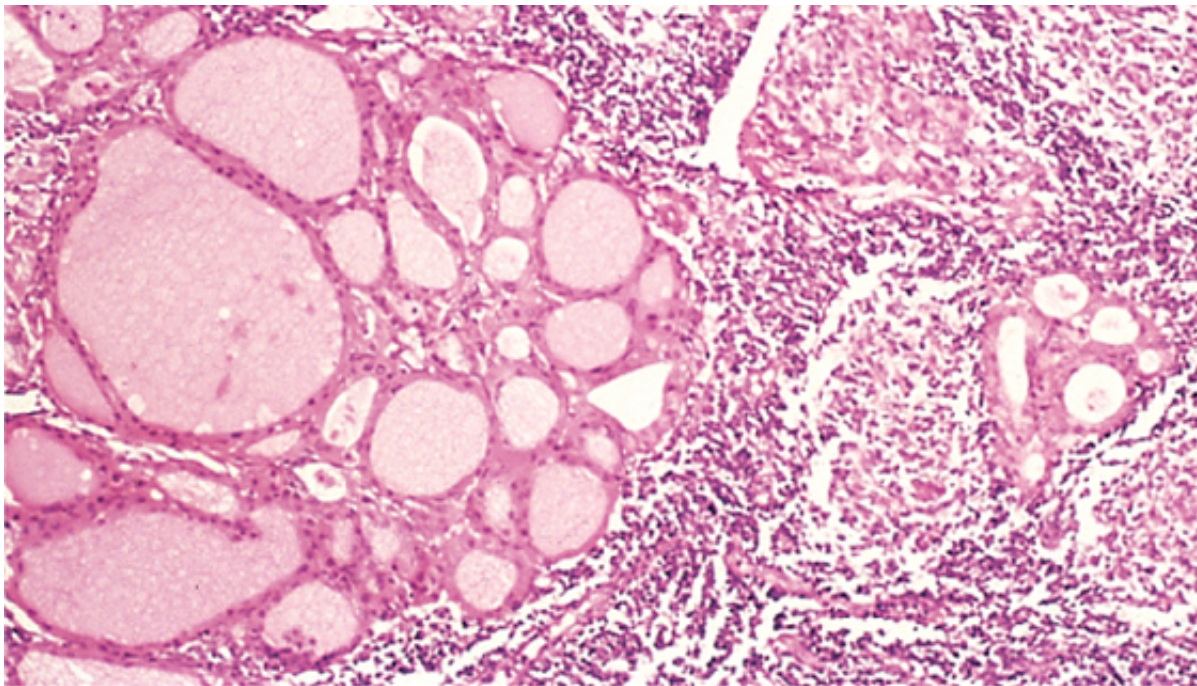
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 Figure 20-7 Pathogenesis of Hashimoto thyroiditis. Sensitization of autoreactive CD4+ helper T cells to thyroid antigens is a proposed mechanism of thyroid cell death. Sensitized CD4+ helper T cells then either differentiate into T<sub>H</sub>1 cells, which mediate a cell-mediated reaction, or stimulate cytotoxic T-cell responses and help B cells (not shown) to develop into an antibody-secreting cell.

There is a significant *genetic component* to disease pathogenesis. Hashimoto thyroiditis occurs with a higher frequency in relatives, and unaffected family members often have circulating thyroid autoantibodies. Associations with *HLA-DR3* and *HLA-DR5* alleles and Hashimoto thyroiditis, but the associations are generally weak. Other genes associated with autoimmune thyroid disease, including genes encoding the T-cell inhibitory receptor CTLA-4, but of uncertain significance.

### Morphology

Grossly, the thyroid is usually diffusely and symmetrically enlarged, although more pronounced enlargement may be seen in some cases. The capsule is intact, and the gland is well demarcated from surrounding structures. The cut surface is pale, gray-tan, firm, and somewhat friable. Microscopically, there is widespread infiltration of the parenchyma by a **mononuclear inflammatory infiltrate** composed of lymphocytes, plasma cells, and well-developed **germinal centers** (Fig. 20-8). The follicles are atrophic and are lined in many areas by epithelial cells distinguished by the presence of eosinophilic, granular cytoplasm, termed **Hürthle**, or **oxyphil, cells**. This is a metaplasia of the normally low cuboidal follicular epithelium to ongoing injury; ultrastructurally the Hürthle cell is characterized by numerous prominent mitochondria. Interstitial connective tissue is abundant. Less commonly, the thyroid is small and atrophic as a result of more extensive destruction (Fig. 20-9, **variant**). Unlike in Reidel thyroiditis, the fibrosis does not extend beyond the capsule.





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Figure 20-8 Photomicrograph of Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate. Follicles lined by deeply eosinophilic Hürthle cells are also seen.

### Clinical Features

Hashimoto thyroiditis comes to clinical attention as *painless enlargement of the thyroid, usually as hypothyroidism*, in a middle-aged woman. The enlargement of the gland is usually symmetric and sufficiently localized to raise a suspicion of neoplasm. In the usual clinical course, hypothyroidism however, it *may be preceded by transient thyrotoxicosis* caused by disruption of thyroid follicles, with release of thyroid hormones ("hashitoxicosis"). During this phase, free  $T_4$  and  $T_3$  concentrations are elevated, TSH uptake is decreased. As hypothyroidism supervenes,  $T_4$  and  $T_3$  levels progressively fall, accompanied by a rise in TSH. Patients with Hashimoto thyroiditis often have *other autoimmune diseases* and are at *increased risk for developing thyroid epithelial neoplasms and Hodgkin lymphomas*. However, there is no established risk for developing thyroid epithelial neoplasms.

### Subacute Granulomatous (de Quervain) Thyroiditis

Subacute granulomatous thyroiditis, also known as de Quervain thyroiditis, is much less common than Hashimoto thyroiditis. It is most common between the ages of 30 and 50 and, like other forms of thyroiditis, occurs in both men and women. Subacute thyroiditis is believed to be caused by a *viral infection* or a postviral inflammatory process. It often follows a history of an upper respiratory infection just before the onset of thyroiditis. In contrast to autoimmune thyroiditis, this process is not self-perpetuating, so the process is limited.

#### Morphology

The gland is firm, with an intact capsule, and may be unilaterally or bilaterally enlarged. The pathology shows disruption of thyroid follicles, with extravasation of colloid leading to a polymorphous inflammatory reaction. The space is replaced over time by lymphocytes, plasma cells, and macrophages. The extravasated colloid elicits a granulomatous reaction, with exuberant giant cells, some containing fragments of colloid. The process ends with resolution of inflammation and fibrosis.

### Clinical Features

The onset of this form of thyroiditis is often acute, characterized by *pain* in the neck (particularly with swallowing) and *variable enlargement of the thyroid*. Transient hyperthyroidism may occur, as in other cases of the disease.



...enlargement of the thyroid. Transient hyperthyroidism may occur, as in other cases of thyroid follicles and release of excessive thyroid hormone. Thyroid function tests are similar to those encountered in other forms of thyroiditis. The leukocyte count and erythrocyte sedimentation rates are increased. Following destruction, a transient hypothyroid phase may ensue. The condition is typically self-limited, with recovery to the normal state within 6 to 8 weeks.

### Subacute Lymphocytic Thyroiditis

Subacute lymphocytic thyroiditis is also known as "silent" or "painless" thyroiditis; in a subset of patients it occurs during pregnancy (*postpartum thyroiditis*). This disease is most likely autoimmune in etiology, because clinical features are similar in the majority of patients. It mostly affects middle-aged women, who present with a *painless* neck swelling and hyperthyroidism. There is an initial phase of thyrotoxicosis (likely to be secondary to thyroid tissue damage and release of thyroid hormone within a few months. Patients with one episode of postpartum thyroiditis are at an increased risk of developing thyroid disease in subsequent pregnancies. In a minority of affected individuals the condition eventually progresses to hypothyroidism. On gross inspection, the thyroid appears normal or slightly enlarged; the histologic features consist of lymphocytic infiltration of the thyroid parenchyma; unlike Hashimoto thyroiditis, follicular atrophy or destruction is not seen.

### Other Forms of Thyroiditis

Two uncommon variants are described here:

*Riedel thyroiditis*, a rare disorder of unknown etiology, is characterized by extensive fibrosis of the thyroid gland and surrounding neck structures. The presence of a hard and fixed thyroid mass clinically simulates a thyroid cancer. The presence of idiopathic fibrosis in other sites in the body, such as the retroperitoneum. The presence of similar features in other patients suggests an autoimmune etiology. *Palpation thyroiditis*, caused by vigorous clinical palpation of the thyroid gland, multifocal follicular disruption associated with chronic inflammatory cells and occasional giant cells. In both forms of thyroiditis, abnormalities of thyroid function are not present, and palpation thyroiditis is usually self-limited and does not require resection for other reasons.

## SUMMARY

**Thyroiditis** Chronic lymphocytic (Hashimoto) thyroiditis is the most common form of thyroiditis in regions where dietary iodine levels are sufficient. Hashimoto thyroiditis is characterized by progressive destruction of thyroid parenchyma, "Hürthle cell change," and lymphoplasmacytic infiltrates, with or without extensive fibrosis. Multiple mechanisms account for Hashimoto disease, including cytotoxicity mediated by thyroid peroxidase (TPO) antibodies, cytokines (IFN- $\gamma$ ), and antithyroid antibodies. Subacute granulomatous (de Quervain) thyroiditis is a self-limited disease, probably secondary to a viral infection, and is characterized by the presence of a granulomatous inflammation in the thyroid. Subacute lymphocytic thyroiditis following a pregnancy (postpartum thyroiditis), is typically painless, and is characterized by lymphocytic inflammation in the thyroid.







## GRAVES DISEASE

In 1835 Robert Graves reported on his observations of a disease characterized by "violent and lorr associated with enlargement of the thyroid gland. *Graves disease is the most common cause of e* characterized by a triad of manifestations:

*Thyrotoxicosis*, caused by a diffusely enlarged, hyperfunctional thyroid, is present in all cas resultant exophthalmos is noted in as many as 40% of patients. A localized, infiltrative *derm myxedema*) is seen in a minority of cases.

Graves disease has a peak incidence between the ages of 20 and 40, with *women being affected than men*. This is a very common disorder that is said to be present in 1.5% to 2.0% of women in important in the causation of Graves disease. An increased incidence of Graves disease occurs a patients, and the concordance rate in monozygotic twins is as high as 60%. As is a recurring ther is a genetic susceptibility to Graves disease associated with the presence of certain HLA haplotyp allelic variants (polymorphisms) in genes encoding the inhibitory T-cell receptor CTLA-4 and the t

### *Pathogenesis*

*Graves disease is an autoimmune disorder* in which a variety of antibodies may be present in the receptor, thyroid peroxisomes, and thyroglobulin. Of these, *autoantibodies to the TSH receptor ar* include:

*Thyroid-stimulating immunoglobulin*: An IgG antibody that binds to the TSH receptor and r adenyl cyclase, with resultant increased release of thyroid hormones. Almost all persons w amounts of this autoantibody to the TSH receptor. This antibody is relatively specific for Gr and thyroid peroxidase antibodies. *Thyroid growth-stimulating immunoglobulins (TGIs)*: Als have been implicated in the proliferation of thyroid follicular epithelium. *TSH-binding inhibi* TSH receptor antibodies prevent TSH from binding normally to its receptor on thyroid epith TBIs mimic the action of TSH, resulting in the stimulation of thyroid epithelial cell activity, v thyroid cell function. It is not unusual to find the coexistence of stimulating *and* inhibiting im patient, a finding that may explain why some patients with Graves disease spontaneously c

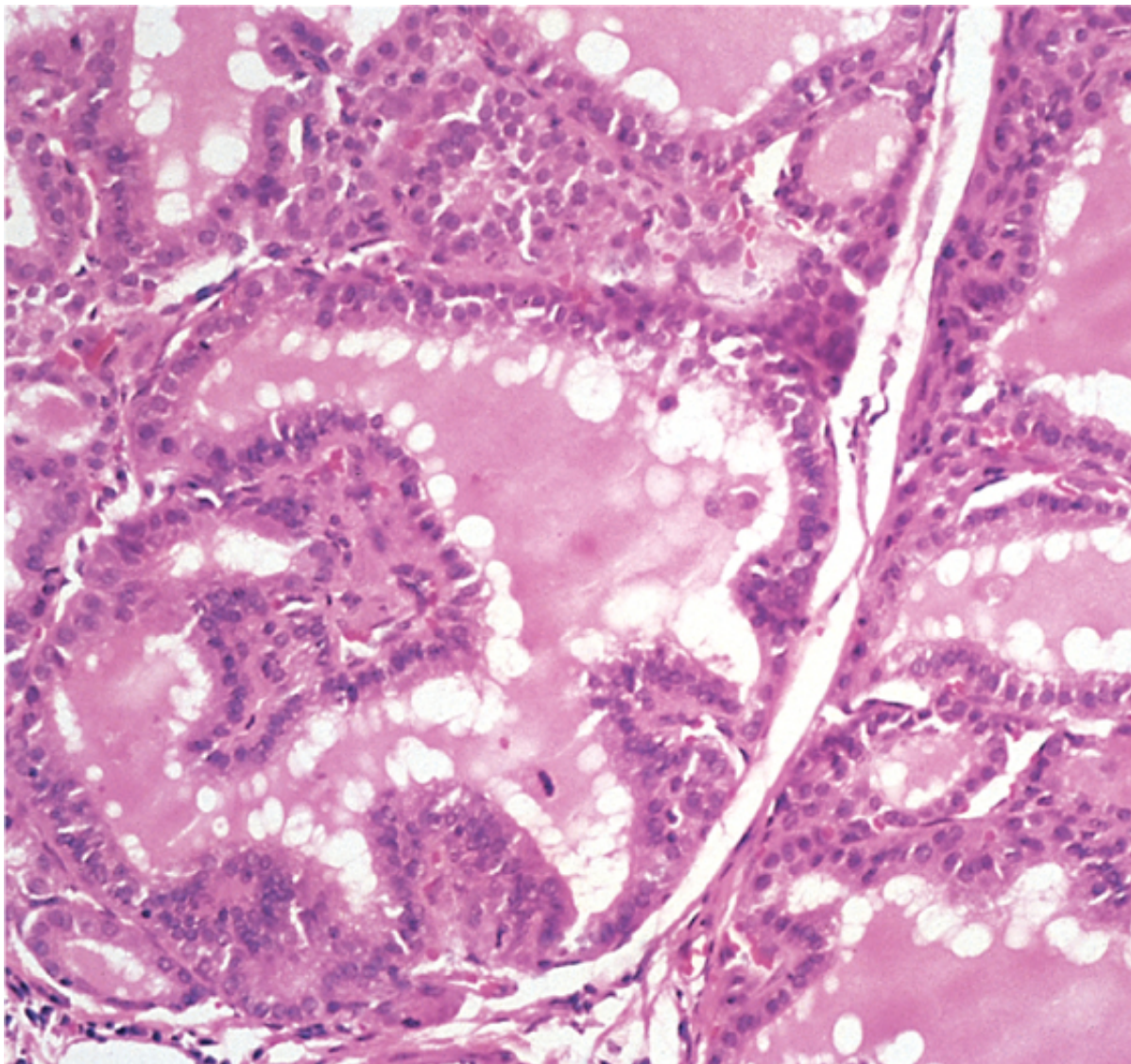
The trigger for the initiation of the autoimmune reaction in Graves disease remains uncertain, alth to be breakdown in helper T-cell tolerance, resulting in the production of anti-TSH autoantibodies. phenomenon is also involved in the development of the *infiltrative ophthalmopathy* characteristic c ophthalmopathy the volume of the retro-orbital connective tissues and extra-ocular muscles is incl including: (1) marked infiltration of the retro-orbital space by mononuclear cells, predominantly T c swelling of extra-ocular muscles; (3) accumulation of extracellular matrix components, specifically hyaluronic acid and chondroitin sulfate; and (4) increased numbers of adipocytes (fatty infiltration) forward and can interfere with the function of the extraocular muscles.

*Autoimmune disorders of the thyroid thus span a continuum in which Graves disease, characteriz one extreme and Hashimoto disease, manifesting as hypothyroidism, occupies the other end*. Sor on preexisting Hashimoto thyroiditis (*hashitoxicosis*), while at other times individuals with Graves thyroid hypofunction; occasionally, families may experience coexistence of Hashimoto and Grave: surprisingly, there is also an element of histologic overlap between the autoimmune thyroid disord intra-thyroidal lymphoid cell infiltrates with germinal center formation). In both disorders the freque as systemic lupus erythematosus, pernicious anemia, type 1 diabetes, and Addison disease, is in

### **Morphology**

In the typical case of Graves disease, the thyroid gland is diffusely enlarged because of **diffuse hypertrophy and hyperplasia** of thyroid follicular epithelial cells. The gland is soft, and its capsule is intact. Microscopically, the follicular epithelial cells are increased in height, columnar, and more crowded than usual. This crowding often results in the formation of papillae that project into the follicular lumen (Fig. 20-9). Such papillae lack fibrovascular cores, a feature that distinguishes them from papillary carcinoma. The colloid within the follicular lumen is pale, with scalloped margins. The interstitium contains infiltrates, consisting predominantly of T cells, with fewer B cells and mature plasma cells throughout the interstitium; germinal centers are common. Preoperative therapy is given to all patients with thyroid disease before surgery. For example, preoperative administration of iodine causes thyroid hypertrophy and hyperplasia of the epithelium and the accumulation of colloid by blocking thyroglobulin secretion; with continued administration, fibrosis of the gland results.

Changes in extra-thyroidal tissues include generalized lymphoid hyperplasia. In Graves ophthalmopathy, the tissues of the orbit are edematous, because of the presence of glycosaminoglycans. In addition, there is infiltration by lymphocytes, mostly T cells. The edema is initially edematous but may undergo fibrosis late in the course of the disease. The disease is also characterized by thickening of the dermis, as a result of deposition of glycosaminoglycans and lymphocyte infiltration.





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Figure 20-9 Photomicrograph of a diffusely hyperplastic gland in a case of Graves disease. The follicles are lined by cuboidal epithelial cells. These cells actively resorb the colloid in the centers of the follicles, resulting in the "scalloped" appearance of the follicle boundaries.

### Clinical Features

The clinical manifestations of Graves disease include those common to all forms of thyrotoxicosis associated uniquely with Graves disease: *diffuse hyperplasia of the thyroid, ophthalmopathy, and thyrotoxicosis* varies from case to case and may sometimes be less conspicuous than other manifestations. Enlargement of the thyroid is present in all cases of Graves disease. The thyroid enlargement is usually asymmetric. Increased flow of blood through the hyperactive gland often produces an audible bruit. Characteristic wide, staring gaze and lid lag. The ophthalmopathy of Graves disease results in exophthalmos (exophthalmos). The extra-ocular muscles are often weak. The exophthalmos may persist or progress with thyrotoxicosis, sometimes resulting in corneal injury. The infiltrative dermopathy, or pretibial myxedema, overlying the shins, where it presents as scaly thickening and induration of the skin. The skin lesions are nodules and often have an orange-peel texture. Laboratory findings in Graves disease include elevated serum TSH. Because of ongoing stimulation of the thyroid follicles by thyroid-stimulating immunoglobulin, uptake is increased and radioiodine scans show a *diffuse uptake* of iodine.

### SUMMARY

**Graves disease** Graves disease, the most common cause of endogenous hyperthyroidism, is characterized by the triad of thyrotoxicosis, ophthalmopathy, and dermopathy. It is an autoimmune disorder caused by activation of thyroid epithelial cells by autoantibodies to the TSH receptor that mimic TSH action. The thyroid in Graves disease is characterized by diffuse hyperplasia of follicles and lymphoid infiltrates; glycosaminoglycan deposits. The ophthalmopathy and dermopathy are characterized by glycosaminoglycan deposits. Laboratory features include elevated serum free  $T_3$  and  $T_4$ , and decreased serum TSH.



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## DIFFUSE AND MULTINODULAR GOITER

Enlargement of the thyroid, or *goiter*, is the most common manifestation of thyroid disease. *Diffuse goiter*, most often caused by dietary iodine deficiency. Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, which, in turn, causes hypertrophy and hyperplasia of thyroid follicular cells and enlargement of the thyroid gland. The compensatory increase in functional mass of the gland is all that is required to ensure a *euthyroid* metabolic state in the vast majority of individuals. If the underlying disorder is a biosynthetic defect, the compensatory responses may be inadequate to overcome the impairment, resulting in *goitrous hypothyroidism*. The degree of thyroid enlargement is proportional to the level and duration of the stimulus and arises in both an endemic and a sporadic distribution.

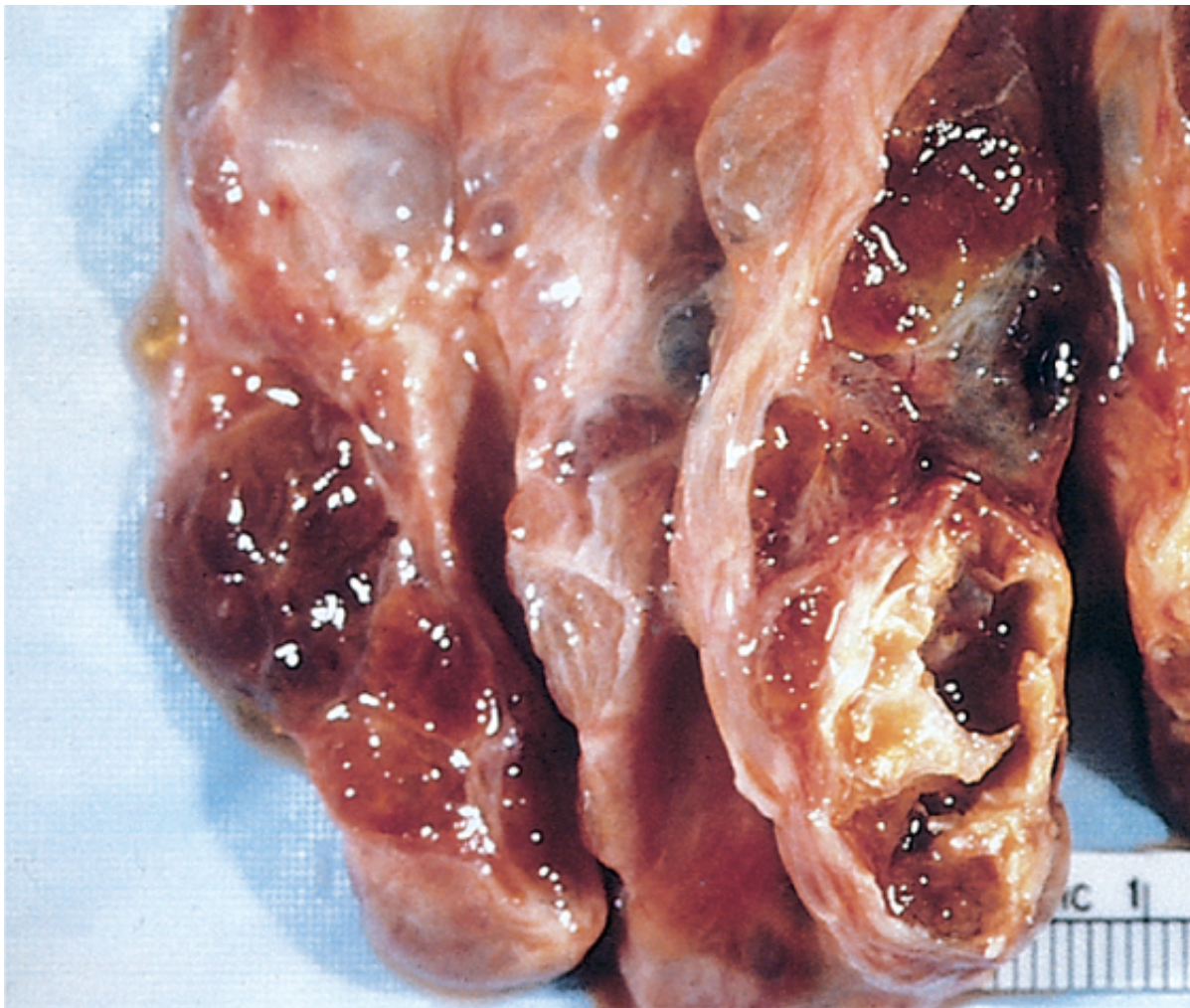
*Endemic goiter* occurs in geographic areas where the soil, water, and food supply contain little iodine. Endemic goiters are present in more than 10% of the population in a given region. Such conditions are present in parts of the world, including the Himalayas and the Andes. With increasing availability of dietary iodine, the prevalence of endemic goiter has declined significantly. *Sporadic goiter* occurs less commonly than endemic goiter, and is more common in females than in males, with a peak incidence in puberty or young adult life, when there is an increase in thyroid hormone requirements. Sporadic goiter may be caused by several conditions, including the ingestion of substances that interfere with thyroid hormone synthesis, such as excessive calcium and vegetables belonging to the Brassicaceae (Cruciferae) (Brussels sprouts, and turnips). In other instances, goiter may result from hereditary enzymatic defects in thyroid hormone synthesis (*dysmorphonogenetic goiter*). In most cases, however, the cause of sporadic goiter is not known.

### Morphology

In most cases, TSH-induced hypertrophy and hyperplasia of thyroid follicular cells result in a symmetric enlargement of the gland (**diffuse goiter**). The follicles are lined by cuboidal epithelial cells, and the colloid may pile up and form projections similar to those seen in Graves disease. If dietary iodine is deficient, or if the demands for thyroid hormone decrease, the stimulated follicular cells may form an enlarged, colloid-rich gland (**colloid goiter**). The cut surface of the thyroid gland is brown, somewhat glassy, and translucent. Microscopically, the follicular epithelium is normal in the early stages of disease or flattened and cuboidal during periods of involution. Colloid is abundant in the latter periods. With time, recurrent episodes of hyperplasia and involution combine to produce an irregular enlargement of the thyroid, termed **multinodular goiter**. Virtually all long-standing diffuse goiters convert into multinodular goiters. They may be nontoxic or may induce thyrotoxicosis (**toxic multinodular goiter**). The pathogenesis of nodules in multinodular goiters has many similarities to that of nodules involved in the formation of benign neoplasm of the thyroid (i.e., follicular adenoma). In the thyroid, thyroid cells are heterogeneous in their response to TSH and their ability to replicate. Some nodules may reflect clonal evolution and subsequent emergence of a clone of cells with a growth advantage. Consistent with this model, both polyclonal and monoclonal nodules occur in multinodular goiter, with the latter presumably having arisen as a result of the acquired genetic abnormality favoring growth. Multinodular goiters are multilobulated, asymmetrically enlarged, and may reach massive size. On the cut surface, irregular nodules containing variable amounts of gelatinous colloid are present (Fig. 20-10). Regressive changes are quite common in multinodular goiters, and include areas of fibrosis, hemorrhage, calcification, and cystic change. The regressive change appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of epithelial hypertrophy and hyperplasia, accompanied by the regressive changes noted in the surrounding tissue.







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 Figure 20-10 Multinodular goiter. The gland is coarsely nodular and contains areas of fibrosis and cystic change. N  
 this condition ("colloid goiter").

### Clinical Features

The dominant clinical features of goiter are those caused by the *mass effects* of the enlarged gland. The problem of a large neck mass, goiters may also cause airway obstruction, dysphagia, and compress the upper thorax. In a minority of patients, a hyperfunctioning ("toxic") nodule may develop within a long-standing goiter, causing *hyperthyroidism*. This condition, known as *Plummer syndrome*, is not accompanied by the infiltrative changes of Graves disease. Less commonly, goiter may be associated with clinical evidence of *hypothyroidism* because of their ability to mask or to mimic neoplastic diseases arising in the thyroid.



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## NEOPLASMS OF THE THYROID

The thyroid gland gives rise to a variety of neoplasms, ranging from circumscribed, benign adenomas to malignant carcinomas. From a clinical standpoint, the possibility of neoplastic disease is of major concern in *nodules*. Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be benign, localized, non-neoplastic conditions (e.g., nodular hyperplasia, simple cysts, or foci of thyroiditis). Malignant nodules are uncommon, accounting for much less than 1% of solitary thyroid nodules. Several clinical criteria for a solitary thyroid nodule:

*Solitary nodules*, in general, are more likely to be neoplastic than are multiple nodules. *Nodules in older patients* are more likely to be neoplastic than are those in younger patients. *Nodules in males* are more likely to be neoplastic than in females. *Nodules in patients with a history of radiation treatment to the head and neck region* is associated with an increased incidence of malignancy. *Hot nodules* (those that take up radioactive iodine in imaging studies) are more likely to be benign than are cold nodules.

Such statistics and general trends, however, are of little significance in the evaluation of a given individual. The possibility of a malignancy, however uncommon, can be life-saving. Ultimately, it is the morphologic evaluation of a nodule by fine-needle aspiration biopsy and histologic study of surgically resected thyroid parenchyma, that determines its nature. In the following sections, we will consider the major thyroid neoplasms, including their clinical features and histologic types.

### Adenomas

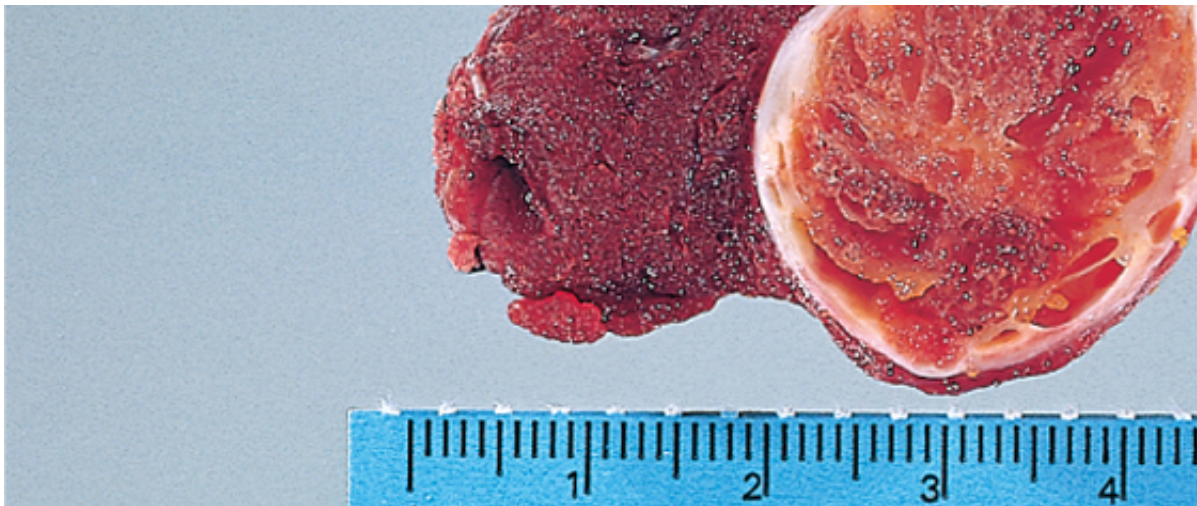
Adenomas of the thyroid are benign neoplasms derived from follicular epithelium. As in the case of other endocrine glands, adenomas are usually solitary. Clinically and morphologically, they may be difficult to distinguish from hyperplastic nodules or, on the other hand, from the less common follicular carcinomas. Although the vast majority of adenomas are non-functional, a small proportion produces thyroid hormones ("toxic adenomas") and causes clinically apparent thyrotoxicosis.

### Pathogenesis

The *TSH receptor signaling pathway* plays an important role in the pathogenesis of toxic adenomas. *Mutations in one of two components of this signaling system*-most often the TSH receptor itself or the *adenylyl cyclase*-cause chronic overproduction of cAMP, generating cells that acquire a growth advantage. This results in the formation of a follicular adenoma, which can autonomously produce thyroid hormone and cause symptoms of thyrotoxicosis. Follicular adenomas have point mutations in the *RAS* family of oncogenes, which have also been identified in follicular carcinomas. This finding has raised the possibility that some adenomas may progress to carcinomas.



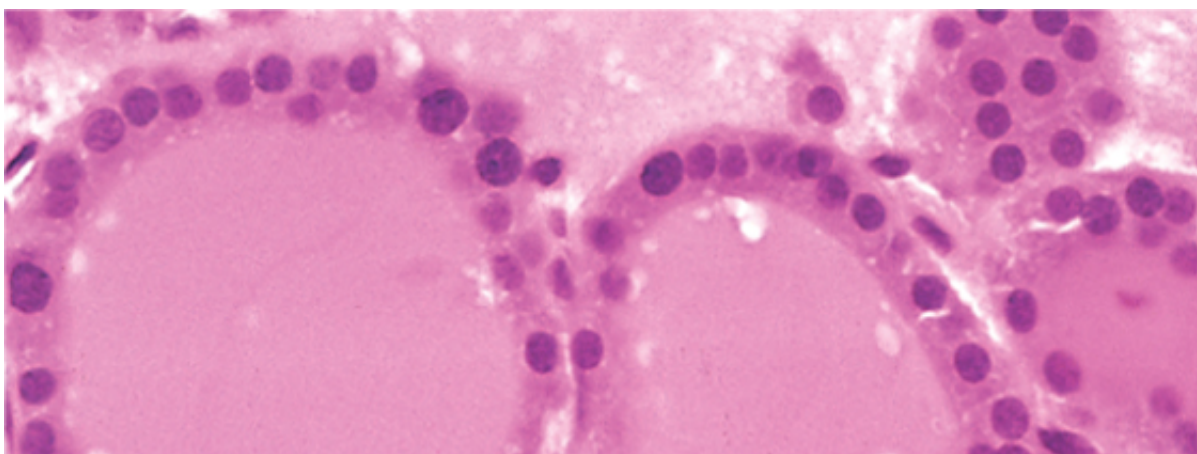


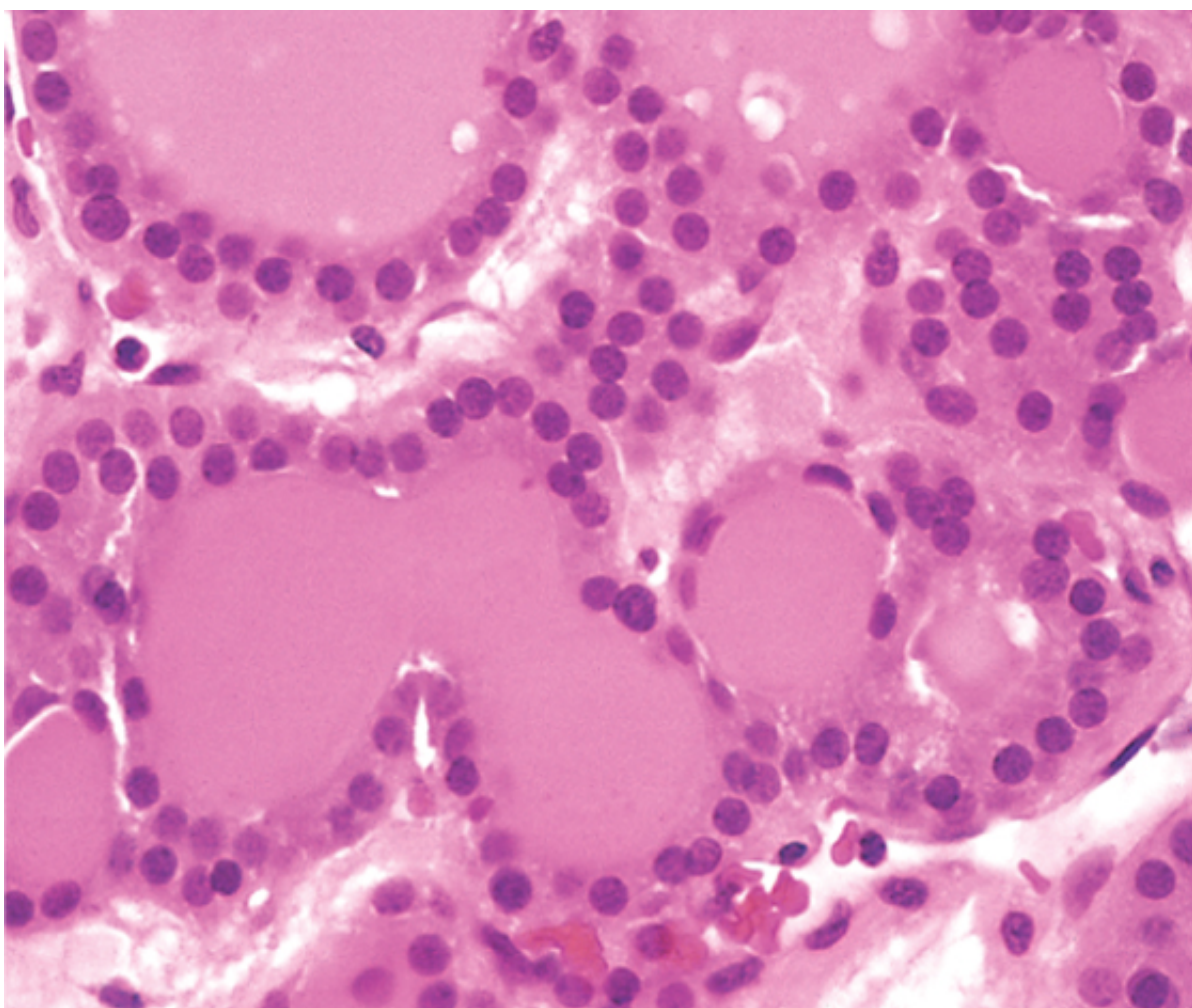


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Figure 20-11 Follicular adenoma of the thyroid. A solitary, well-circumscribed nodule.

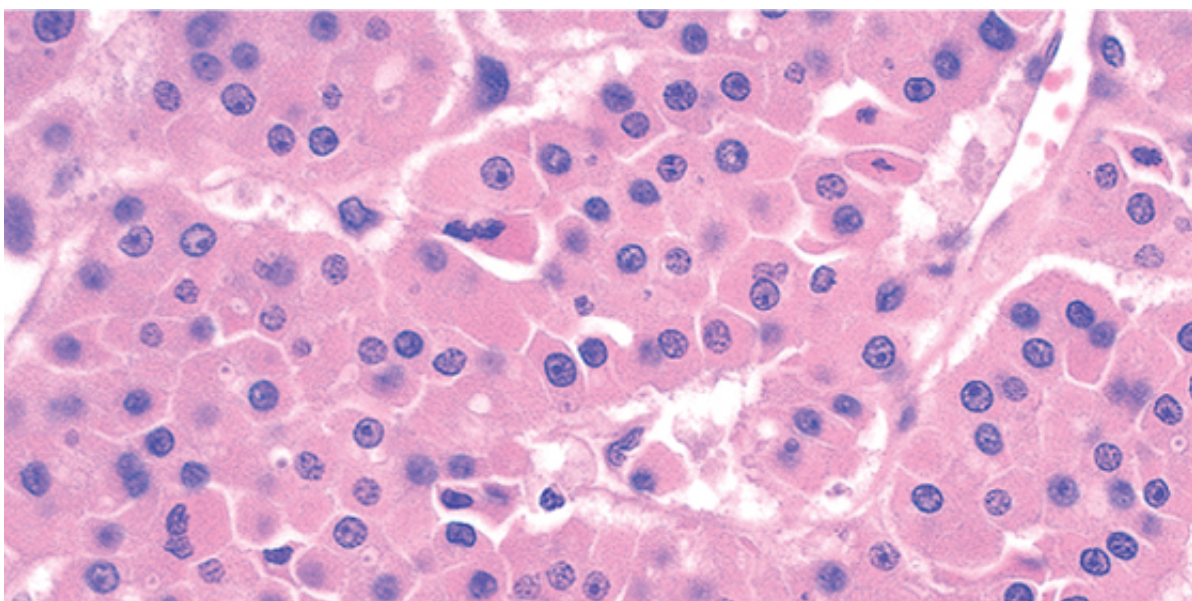
### Morphology

The typical thyroid adenoma is a **solitary**, spherical lesion that compresses the adjacent thyroid. The neoplastic cells are demarcated from the adjacent parenchyma by a **well-formed capsule** (Fig. 20-11). **These features are important in making the distinction from hyperplastic nodules**, which contain multiple nodules on their cut surface (even though the patient may present with a solitary dominant nodule), do not demonstrate compression of the adjacent thyroid, and lack a well-formed capsule. Microscopically, the constituent cells are arranged in uniform follicles filled with colloid (Fig. 20-12). The follicular growth pattern within the adenoma is usually quite similar to that of the adjacent non-neoplastic thyroid, and this is another distinguishing feature from multinodular and uninvolved thyroid parenchyma demonstrate comparable growth patterns. However, the presence of a well-formed capsule is not a typical feature of adenomas and, if present, should raise the suspicion of an adenoma. The neoplastic cells are uniform, with well-defined cell borders. In some cases, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (oxyphil or Hürthle cells) (Fig. 20-13); the clinical presentation and behavior of a **Hürthle cell adenoma** are no different from those of a conventional adenoma. Similar to endocrine tumors at other anatomic sites, even Hürthle cell adenomas may, on occasion, exhibit focal nuclear pleomorphism, atypia, and prominent nucleoli. However, the presence of these features itself does not constitute a feature of malignancy. The hallmark of all follicular adenomas is the presence of an intact well-formed capsule encircling the tumor. **Careful evaluation of the capsule is therefore critical in the distinction of follicular adenomas from follicular carcinomas.** Follicular carcinomas demonstrate capsular and/or vascular invasion (see below).

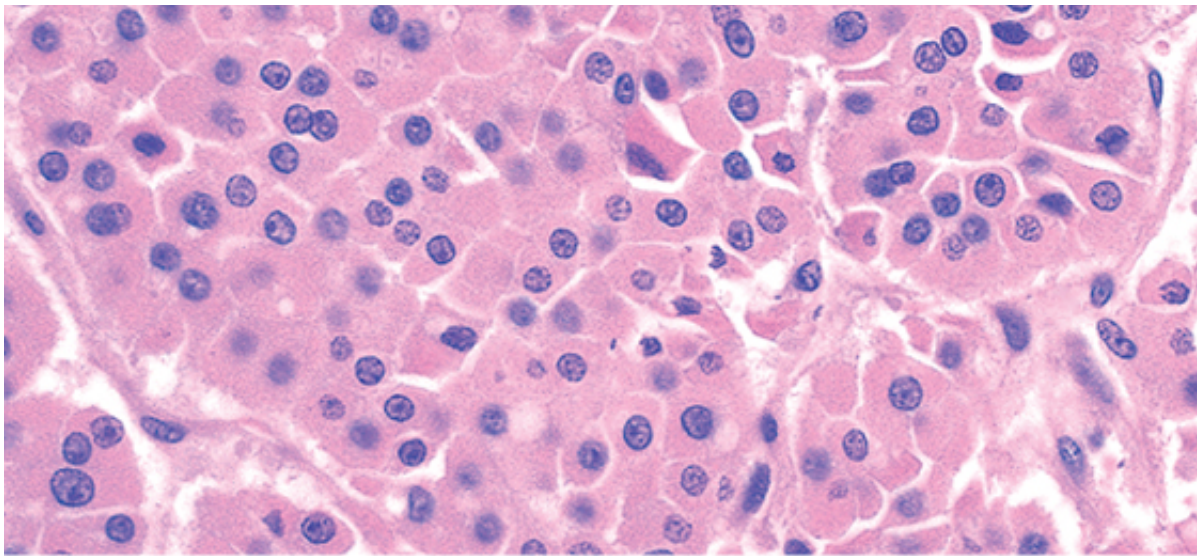




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 Figure 20-12 Photomicrograph of follicular adenoma. Well-differentiated follicles resemble normal thyroid follicles.







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Figure 20-13 Hürthle cell adenoma. A high-power view showing that the tumor is composed of cells with abundant (Courtesy of Dr. Mary Sunday, Brigham and Women's Hospital, Boston, Mass)

### *Clinical Features*

Most adenomas of the thyroid present as painless nodules, often discovered during a routine physical examination. They may produce local symptoms such as difficulty in swallowing. As previously stated, persons with toxic adenomas may develop thyrotoxicosis. After injection of radioactive iodine, most adenomas take up iodine less avidly than normal thyroid tissue. On radionuclide scanning, therefore, adenomas appear as "cold" nodules relative to the adjacent normal thyroid tissue. However, some adenomas, which will appear as "warm" or "hot" nodules in the scan. As many as 10% of "cold" nodules are malignant. In contrast, malignancy is virtually nonexistent in "hot" nodules. Additional techniques used in the preoperative evaluation of thyroid adenomas are ultrasonography and fine-needle aspiration biopsy. Because of the need for evaluation, the diagnosis of thyroid adenoma can only be made after careful histologic examination of the resected specimen. Most thyroid adenomas are therefore removed surgically to exclude malignancy. Thyroid adenomas have an excellent prognosis and rarely metastasize.

### **Carcinomas**

Clinically significant carcinomas of the thyroid are relatively uncommon in the United States, being responsible for about 1% of all cancer-related deaths; in contrast, it is not unusual to detect a microscopic (clinically silent) tumor as an incidental finding on autopsy. In contrast, of thyroid carcinoma occur in adults, although some forms, particularly papillary carcinomas, may occur in children. The incidence of thyroid carcinoma has increased in the early and mid decades of the 20th century. The expression of estrogen receptors on neoplastic thyroid epithelium. In contrast, cases presenting in children are distributed equally among males and females, largely related to exogenous influences (see later). The relative frequencies of the various types and their relative frequencies are as follows:

Papillary carcinoma (75% to 85% of cases) Follicular carcinoma (10% to 20% of cases) Medullary carcinoma (5% to 10% of cases) Anaplastic carcinomas (<5% of cases)

Most thyroid carcinomas are derived from the follicular epithelium, except for medullary carcinomas, which are derived from the parafollicular, or C, cells. Because of the unique clinical and biologic features associated with each subtype, they will be described separately, after discussion of pathogenesis.

### *Pathogenesis*

Both genetic and environmental variables are implicated in the pathogenesis of thyroid cancers.

#### Genetic Variables

Genetic influences are implicated in both familial and nonfamilial ("sporadic") forms of thyroid cancer, account for most inherited cases of thyroid cancer, while familial papillary and follicular cancers are the pathogenesis of individual histologic variants.

**Papillary thyroid carcinomas:** Two major types of genetic alterations—chromosomal rearrangements in the pathogenesis of papillary thyroid carcinomas. Notably, these alterations lead to activation of the mitogen-activating protein (MAP) kinase signaling pathway—and therefore occur in nonoverlapping rearrangements involving the tyrosine kinase receptor gene *RET* (located on chromosome 10q24) in papillary thyroid carcinomas. Such rearrangements result in the formation of novel fusion genes (e.g., *RET/PTC*), which constitutively activate *RET* and the downstream MAP kinase signaling pathway. The frequency of *RET* rearrangements is significantly higher in papillary cancers arising in children and in the background of radiation exposure. The protein encoded by *RET* is a receptor tyrosine kinase that plays essential roles in the development of neurons (neurotrophic tyrosine kinase receptor 1, located on chromosome 1q) is similarly rearranged in neuroblastoma. In contrast to these chromosomal rearrangements, approximately a third to a half of papillary carcinomas harbor point mutations in the *BRAF* oncogene, which also activate the MAP kinase signaling pathway. Approximately one-half of follicular thyroid carcinomas harbor mutations in the *RAS* family (e.g., *KRAS*). Recently, a unique translocation has been described between *PAX8*, a paired homeobox gene involved in development, and the gene encoding peroxisome proliferator-activated receptor  $\gamma$ 1 (*PPAR* $\gamma$ 1) implicated in terminal differentiation of cells. The *PAX8-PPAR* $\gamma$ 1 fusion is present in approximately 50% of papillary thyroid carcinomas, specifically those cancers with a t(2;3)(q13;p25) translocation, which permits junction of the two genes. Follicular carcinomas seem to arise by two distinct and virtually nonoverlapping molecular pathways: one by mutation or a *PAX8-PPAR* $\gamma$ 1 fusion; rarely are both genetic abnormalities present in the same tumor. Medullary carcinomas arise from the parafollicular C cells in the thyroid. Familial medullary thyroid carcinoma (endocrine neoplasia type 2 (see below), and are associated with germ-line *RET* proto-oncogene mutations. *RET* mutations are also seen in nonfamilial (sporadic) medullary thyroid carcinomas. *RET* rearrangements such as *ret/PTC* translocations, reported in papillary cancers, are not seen in medullary carcinomas. These highly aggressive and lethal tumors can arise de novo or by dedifferentiation from a follicular carcinoma. Inactivating point mutations in the *p53* tumor suppressor gene are rare in thyroid carcinomas but common in anaplastic tumors.

### Environmental Variables

Exposure to ionizing radiation, particularly during the first 2 decades of life, has emerged as one of the most important predisposing factors to the development of thyroid cancer. In the past, radiation therapy was liberally used to treat neck lesions in infants and children, including reactive tonsillar enlargement, acne, and tinea capitis. Such treatment during childhood subsequently developed thyroid malignancies, usually several decades later. The risk of developing carcinoma of the thyroid is substantially higher, in addition, among atomic bomb survivors in Japan and among residents of the area around the Chernobyl nuclear plant disaster. *The overwhelming majority of cancers arising after radiation exposure are papillary carcinomas, and most have RET gene rearrangements.* Long-standing multinodular goiter has been associated with thyroid cancer in some cases, since areas with iodine deficiency-related endemic goiter have a higher prevalence of thyroid cancer.

### Papillary Carcinoma

As mentioned above, papillary carcinomas represent the most common form of thyroid cancer. They account for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

#### Morphology

Papillary carcinomas may present as solitary or multifocal lesions within the thyroid gland. They are usually well circumscribed and even encapsulated; in other instances, they infiltrate the surrounding thyroid tissue with ill-defined margins. The lesions may contain areas of fibrosis and calcification. On gross examination, the cut surface, they may appear granular and may sometimes contain grossly discrete nodules (Fig. 20-14A). The definitive diagnosis of papillary carcinoma can be made only after microscopic examination. The currently used, **the diagnosis of papillary carcinoma is based on nuclear features** of the tumor cells. The nuclei of papillary carcinoma cells contain very finely granular chromatin, which imparts an **optically clear** appearance, giving rise to the designation "ground-glass" nuclei.

nuclei (Fig. 20-14C, D). In addition, invaginations of the cytoplasm may give the appearance of inclusions (hence the term **pseudo-inclusions**) in cross-sections. A **papillary architecture** is seen in many cases (Fig. 20-14B), although some tumors are composed predominantly of follicles. These **follicular variants** still behave biologically as papillary carcinomas if they have the characteristic nuclear features described. When present, the papillae of papillary carcinoma differ from those seen in hyperplastic lesions. Unlike hyperplastic papillary lesions, the neoplastic papillae have dense fibrovascular cores. Calcified structures termed **psammoma bodies** are often present within the papillae. Permeation by tumor is often present, but invasion of blood vessels is relatively uncommon in smaller lesions. Metastases to adjacent cervical lymph nodes are estimated to occur in about 50% of cases.

### *Clinical Features*

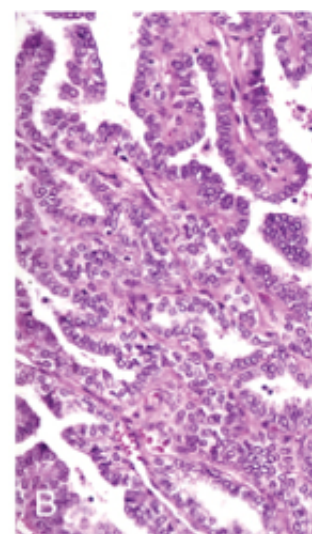
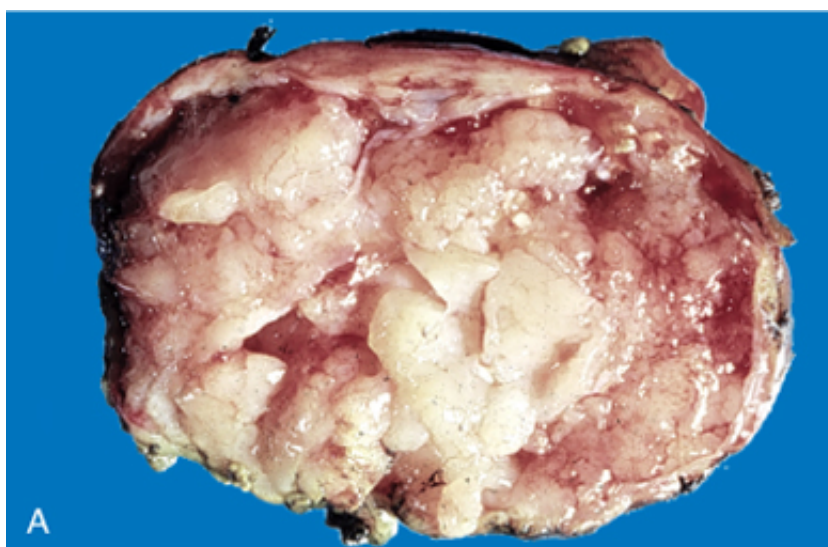
Papillary carcinomas are nonfunctional tumors, and thus they present most often as a painless mass in the neck. The presence of isolated cervical nodal metastases, intermediate in size, has little influence on the generally good prognosis of these lesions. In a minority of patients, however, the time of diagnosis, most commonly to the lung. Papillary carcinomas are indolent lesions, with a long natural history. In general, the prognosis is less favorable among elderly persons and in patients with invasion of lymph nodes or distant metastases.

### **Follicular Carcinoma**

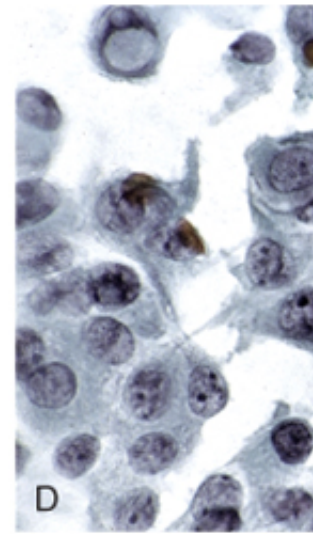
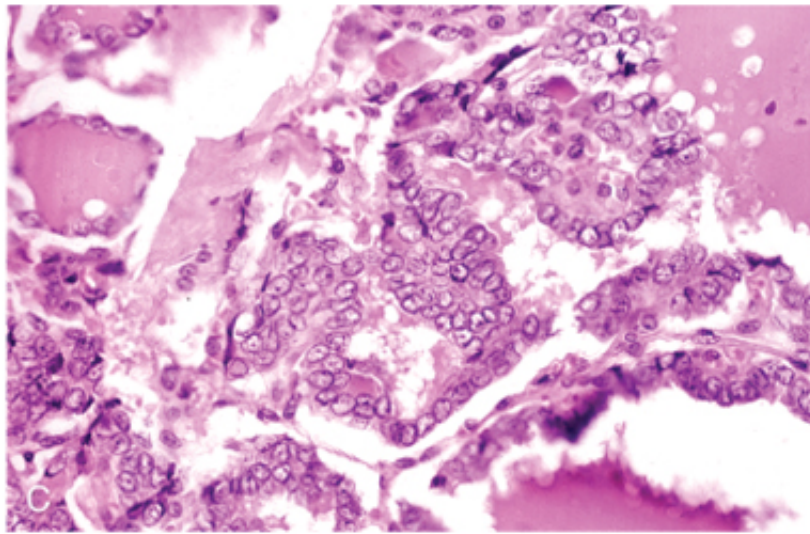
Follicular carcinomas are the second most common form of thyroid cancer. They usually present as painless masses in the neck. The incidence of follicular carcinoma is higher in patients with iodine deficiency, suggesting that, in some cases, nodular goiter may predispose to the development of follicular carcinoma. The finding of mutations in follicular adenomas and carcinomas suggests that they may be related tumors.

### **Morphology**

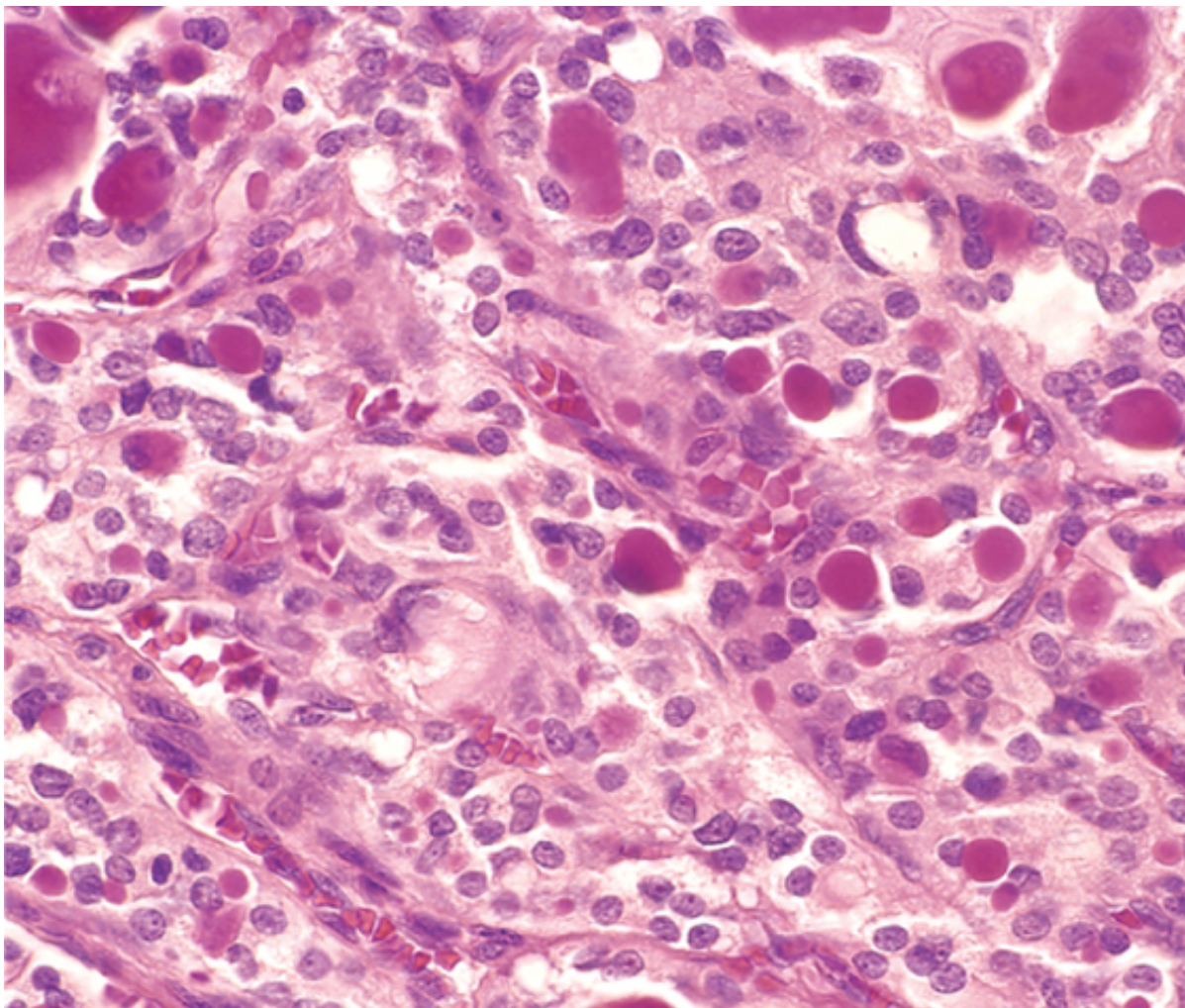
Microscopically, most follicular carcinomas are composed of fairly uniform cells and are often well circumscribed, but they are not encapsulated (Fig. 20-15); in other cases, follicular differentiation is absent. Similar to follicular adenomas, Hürthle cell variants of follicular carcinomas may be seen. Follicular carcinomas may be grossly infiltrative or minimally invasive. The latter are sharply circumscribed and may be impossible to distinguish from follicular adenomas on gross examination. **To avoid false-negative results, extensive histologic sampling of the tumor-capsule-thyroid interface, to exclude vascular invasion (Fig. 20-16).** Extensive invasion of adjacent thyroid parenchyma is characteristic of follicular carcinoma obvious in some cases. As mentioned earlier, follicular lesions in which the cells have the nuclear features typical of papillary carcinomas should be regarded as papillary cancers.



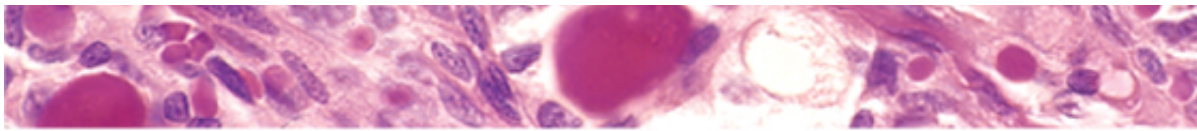




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 Figure 20-14 Papillary carcinoma of the thyroid. **A**, A papillary carcinoma with grossly discernible papillary structure  
 papillae (**B**), lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie eye" nuclei  
 of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells. (Courtesy  
 University of Texas Southwestern Medical School, Dallas, Texas.)





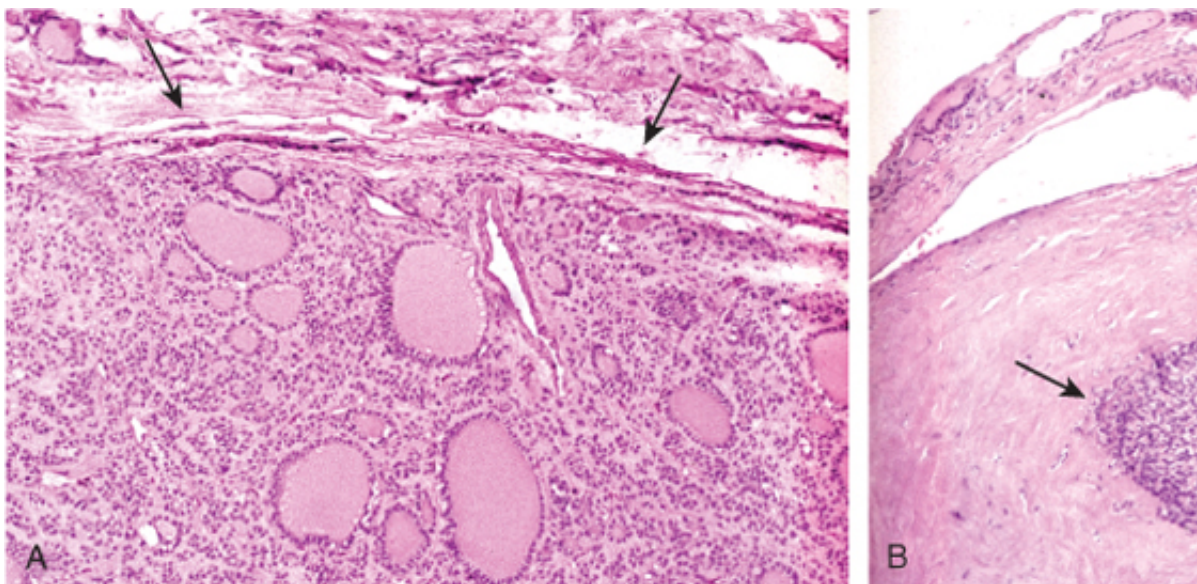


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Figure 20-15 Follicular carcinoma of the thyroid. A few of the glandular lumens contain

### Clinical Features

Follicular carcinomas present most frequently as solitary "cold" thyroid nodules. In rare cases, the neoplasms tend to metastasize through the bloodstream to the lungs, bone, and liver. Regional neoplasms contrast to papillary carcinomas. Follicular carcinomas are treated with surgical excision. Well-differentiated thyroid carcinomas are treated with radioactive iodine, which can be used to identify, and ablate, such lesions. Because better differentiated patients are usually treated with thyroid hormone after surgery to suppress endogenous TSH.

### Medullary Carcinoma



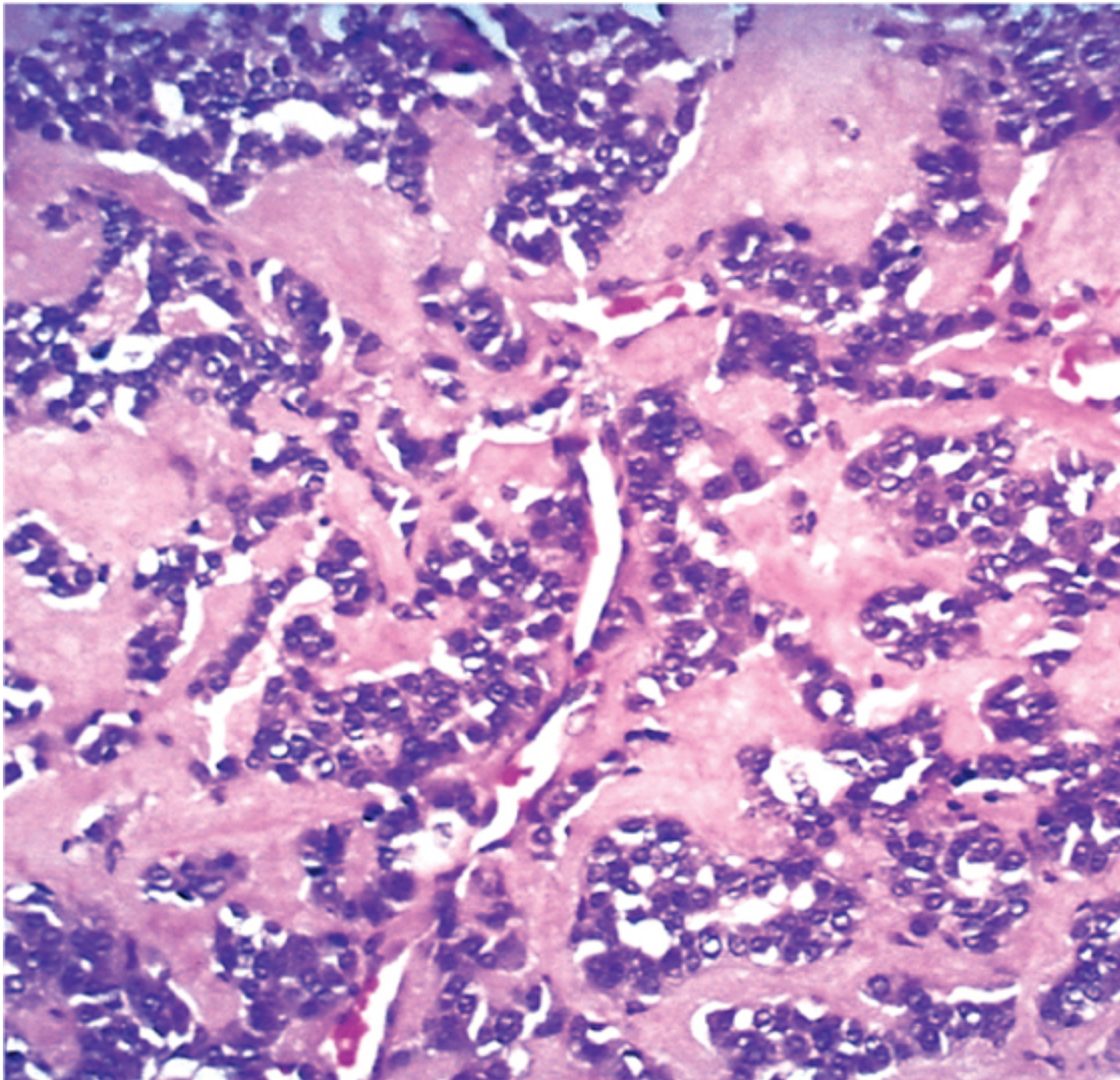
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Figure 20-16 Capsular invasion in follicular carcinoma. Evaluating the integrity of the capsule is critical in distinguishing follicular carcinomas. In adenomas (A), a fibrous capsule, usually thin but occasionally more prominent, surrounds the neoplasm (arrows); compressed normal thyroid parenchyma is usually present external to the capsule (top). B, In contrast, follicular carcinomas (arrows) that may be minimal, as in this case, or widespread with extension into local structures.

Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular normal C cells; medullary carcinomas secrete calcitonin, the measurement of which plays an important role in the postoperative follow-up of patients. In some cases, the tumor cells elaborate other polypeptide hormones, such as vasoactive intestinal peptide (VIP). Medullary carcinomas arise *sporadically* in about 80% of cases occurring in the setting of MEN syndromes 2A or 2B, or familial medullary thyroid carcinoma syndrome, as discussed later. Recall that both familial and sporadic medullary forms demonstrate medullary carcinomas, as well as FMTC, occur in adults, with a peak incidence in the fifth to sixth decades; in contrast, occur in younger patients and may even arise in children.

### Morphology

Medullary carcinomas may arise as a solitary nodule or may present as multiple lesions throughout the thyroid. **Multicentricity** is particularly common in familial cases. Larger lesions may show necrosis and hemorrhage and may extend through the capsule of the thyroid. Microscopically, medullary carcinomas are composed of polygonal to spindle-shaped cells, which may form nests or cords.

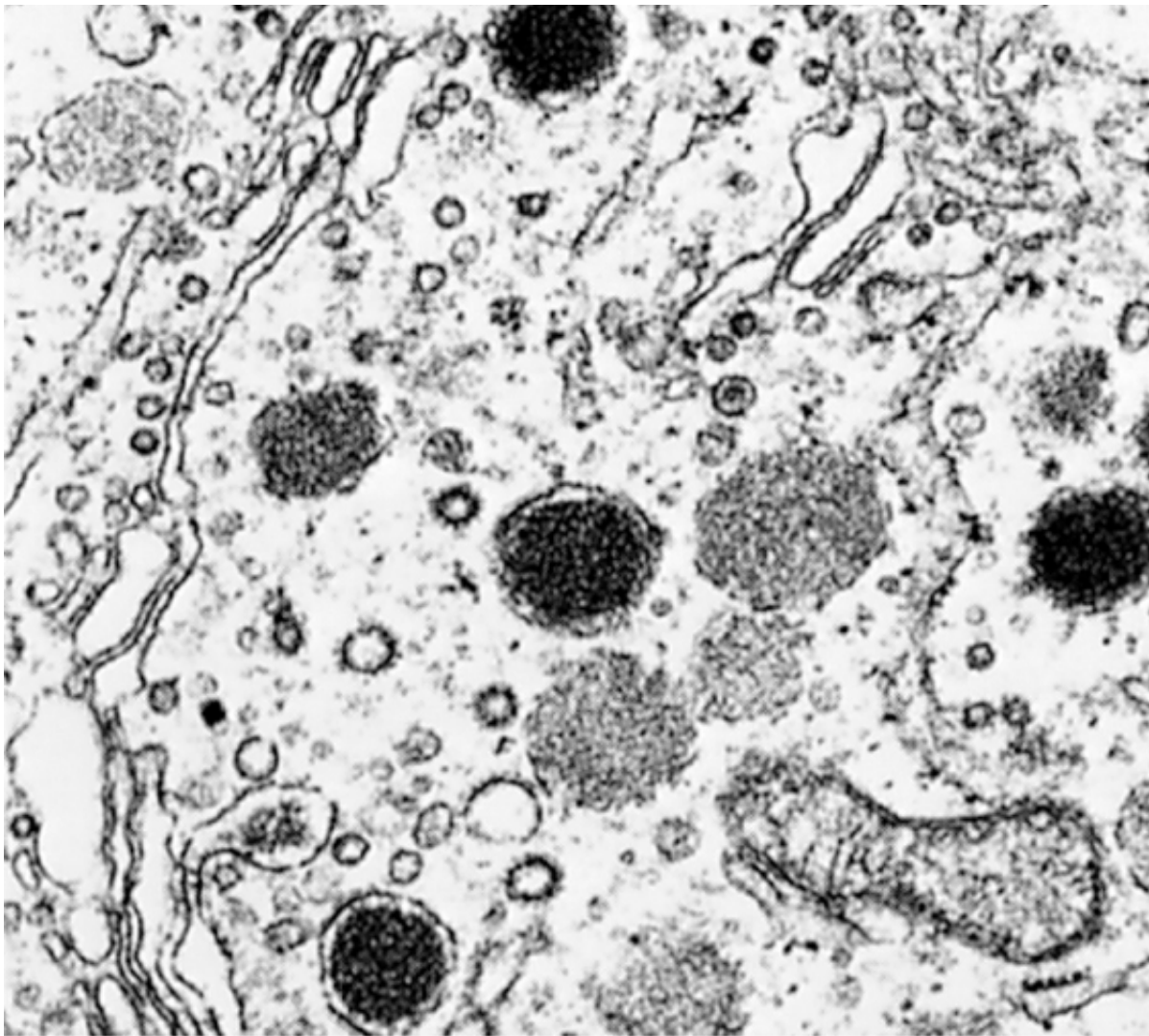
carcinomas are composed of polygonal to spindle shaped cells, which may form follicles. Acellular **amyloid deposits**, derived from altered calcitonin molecules, are found in the stroma in many cases (Fig. 20-17) and are a distinctive feature of these tumors. Calcitonin is demonstrable both within the cytoplasm of the tumor cells and in the stromal amyloid by immunohistochemical methods. Electron microscopy reveals variable numbers of intraluminal membrane-bound electron-dense granules (Fig. 20-18). One of the peculiar features of medullary carcinomas is the presence of **multicentric C-cell hyperplasia** in the surrounding thyroid tissue, a feature usually absent in sporadic lesions. While the precise criteria for defining what constitutes C-cell hyperplasia are variable, the presence of multiple prominent clusters of C cells scattered throughout the thyroid should raise the specter of a familial tumor, even if that history is not available. Follicular hyperplasia is believed to represent the precursor lesions from which medullary carcinomas arise.



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Figure 20-17 Medullary carcinoma of the thyroid. These tumors typically contain amyloid, visible here as homogeneously pink molecules secreted by the neoplastic cells.







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 Figure 20-18 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory and other peptides (original magnification  $\times 30,000$ ).

### ***Clinical Features***

Sporadic cases of medullary carcinoma present most often as a mass in the neck, sometimes associated with dysphagia or hoarseness. In some instances the initial manifestations are caused by the secretory products (e.g., diarrhea caused by the secretion of VIP). Notably, hypocalcemia is not a feature, despite the presence of relatively elevated calcitonin levels or *RET* mutations permits early detection of tumors in families. In fact, all MEN-2 kindred carrying *RET* mutations are offered prophylactic thyroidectomies to prevent the development of medullary carcinomas; often, the only histologic finding in the resected thyroid of these asymptomatic carriers is a small (<1 cm) "micromedullary" carcinomas. Recent studies have shown that specific *RET* mutations are associated with medullary carcinomas.

### ***Anaplastic Carcinoma***

Anaplastic carcinomas of the thyroid are among the most aggressive human neoplasms, with a median survival time of less than 6 months. Anaplastic carcinomas are older than those with other types of thyroid cancer, with a mean age of 65 years. They often arise in the setting of a long history of multinodular goiter, whereas 20% of the patients with these tumors have a history of differentiated thyroid cancer. About 30% have a concurrent differentiated thyroid tumor, frequently a papillary carcinoma. These findings suggest that anaplastic carcinoma develops by "dedifferentiation" from more differentiated tumors as a result of ongoing genetic and epigenetic changes.

carcinoma develops by dedifferentiation from more differentiated tumors as a result of one or more mutations in the function of the *p53* tumor suppressor gene.

### **Morphology**

Anaplastic carcinomas present as bulky masses that typically grow rapidly beyond adjacent neck structures. Microscopically, these neoplasms are composed of high-grade cells and may take on several histologic patterns, including (1) large, pleomorphic **giant cell** sarcomatous appearance; (2) **mixed** spindle and giant-cell lesions; and (3) **small cell** pattern, as seen in small-cell carcinomas at other sites. It is unlikely that a true small-cell carcinoma exists in the thyroid and most of the "anaplastic small-cell" tumors ultimately proved to be medullary carcinoma. Foci of papillary or follicular differentiation may be present in some tumors arising from a better differentiated carcinoma.

### **Clinical Features**

Anaplastic carcinomas grow with wild abandon despite therapy. Metastases to distant sites are common within less than 1 year as a result of aggressive local growth and compromise of vital structures in the neck.

### **SUMMARY**

**Thyroid Neoplasms** Most thyroid neoplasms present as solitary thyroid nodules. Follicular adenomas are the most common benign neoplasms, and follicular carcinoma is the most common malignancy. Multiple genetic pathways are involved in thyroid carcinogenesis. Some of the genetic abnormalities that are fairly unique to thyroid carcinomas include the *PAX8-PPAR $\gamma$ 1* fusion (in follicular carcinoma), chromosomal rearrangements involving the *RET* oncogene (papillary cancers), and mutations of *RET* (medullary carcinomas). Both follicular and medullary carcinomas are composed of well-differentiated follicular epithelial cells, but the latter show evidence of capsular and/or vascular invasion. *Papillary carcinoma* is characterized by nuclear features (ground-glass nuclei, pseudo-inclusions) even in the absence of capsular invasion. Psammoma bodies are a characteristic feature of papillary cancers; these nodules may metastasize via lymphatics but their prognosis is excellent. *Medullary carcinoma* arises from the parafollicular C cells and can occur in either sporadic (20%) or familial (5-10%) settings. Multicentricity and C-cell hyperplasia are features of familial medullary carcinoma. *Anaplastic carcinomas* are thought to arise from either follicular or medullary neoplasms. They are highly aggressive, uniformly lethal







## PARATHYROID GLANDS

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The parathyroid glands are derived from the developing pharyngeal pouches that also give rise to the thymus. They normally lie in close proximity to the upper and lower poles of each thyroid lobe, but they may be found anywhere along the pathway of descent of the pharyngeal pouches, including the carotid sheath and the thymus and elsewhere in the anterior mediastinum. Most of the gland is composed of *chief cells*. The chief cells vary from light to dark pink with H&E stains, depending on their glycogen content. They contain secretory granules of *parathyroid hormone (PTH)*. *Oxyphil cells* are found throughout the normal parathyroid either singly or in small clusters. They are slightly larger than the chief cells, have acidophilic cytoplasm, and are tightly packed with mitochondria. *The activity of the parathyroids is controlled by the level of free (ionized) calcium in the bloodstream rather than by trophic hormones secreted by the hypothalamus and pituitary.* Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH, which in turn:

Activates osteoclasts, thereby mobilizing calcium from bone  
Increases the renal tubular reabsorption of calcium  
Increases the conversion of vitamin D to its active dihydroxy form in the kidneys  
Increases urinary phosphate excretion  
Augments gastrointestinal calcium absorption.

The net result of these activities is an increase in the level of free calcium, which inhibits further PTH secretion. Abnormalities of the parathyroids include both hyperfunction and hypofunction. *Tumors of the parathyroid glands, unlike thyroid tumors, usually come to attention because of excessive secretion of PTH rather than mass effects.*



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## HYPERPARATHYROIDISM

Hyperparathyroidism occurs in two major forms, *primary* and *secondary*, and, less commonly, as a *tertiary* condition. The former represents an autonomous, spontaneous overproduction of PTH, while the latter two conditions are phenomena in individuals with chronic renal insufficiency.

### Primary Hyperparathyroidism

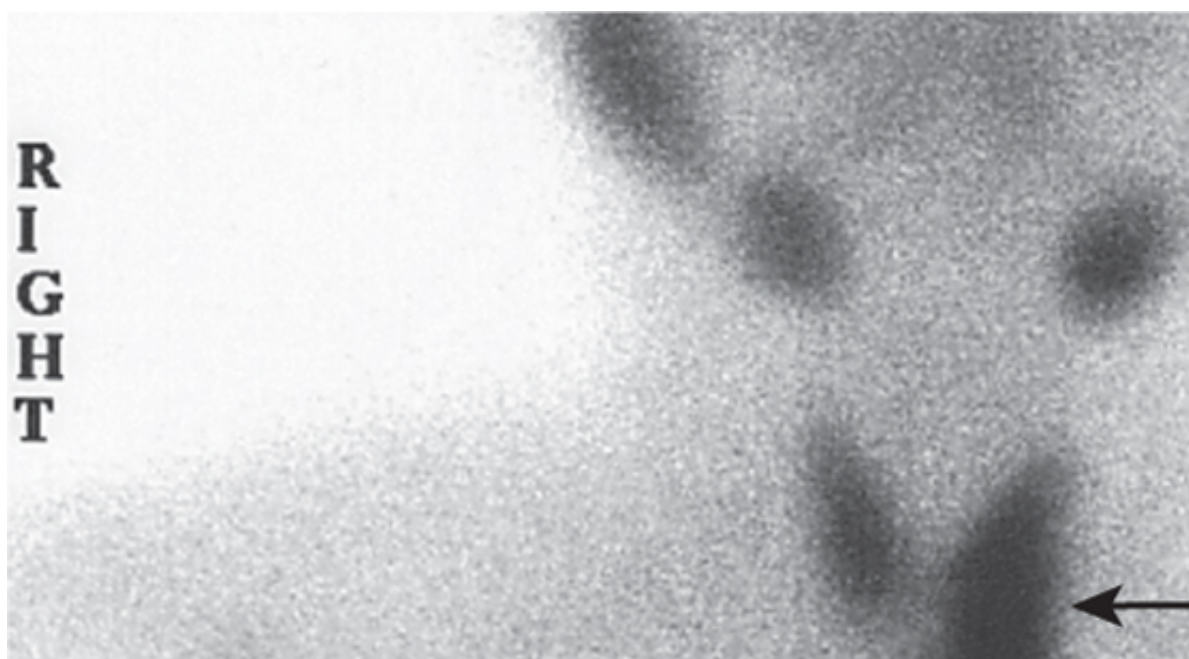
Primary hyperparathyroidism is one of the most common endocrine disorders, and it is an important one because of the dramatic increase in the detection of cases beginning in the latter half of the last century, resulting from the availability and use of advanced analyzers for detecting serum electrolytes. The frequency of occurrence and the underlying hyperfunction is as follows:

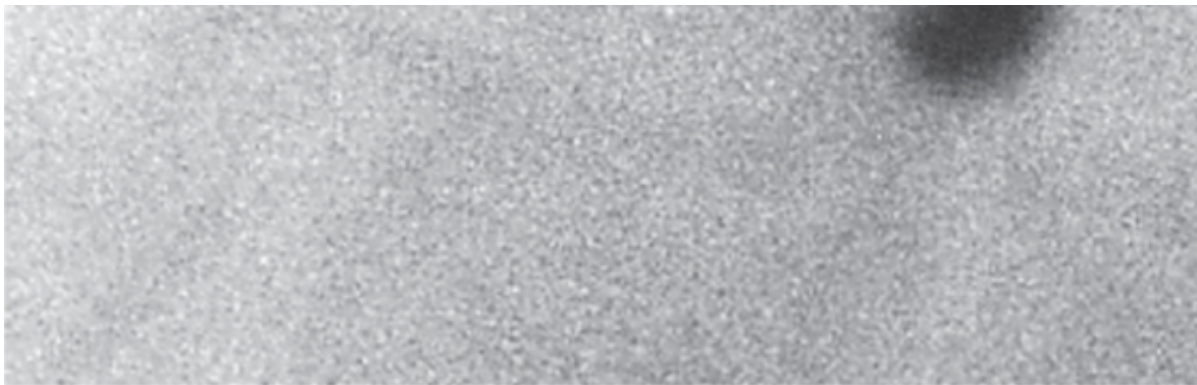
Adenoma-75% to 80% Primary hyperplasia (diffuse or nodular)-10% to 15% Parathyroid carcinoma-1% to 2%

In more than 95% of cases, primary hyperparathyroidism is caused by sporadic parathyroid adenoma. Genetic defects identified in familial primary hyperparathyroidism include multiple endocrine neoplasia type 2A (MEN-2A) (see below). Familial hypocalciuric hypercalcemia is a rare cause of hyperparathyroidism. A mutation in the calcium-sensing receptor (*CASR*) gene on parathyroid cells, leading to constitutive PTH secretion.

### Molecular Pathogenesis of Parathyroid Tumors

Although the detailed discussion of genetic alterations in parathyroid tumors is beyond the scope of this chapter, the abnormalities are commonly associated with these tumors will be mentioned. The first of these, *cyclin D1* (also known as *adenomatosis gene 1*), is located on chromosome 11q. The protein product of *PRAD1* belongs to the cyclins (hence the protein is named cyclin D1). Overexpression of cyclin D1 is common in parathyroid adenoma as well as in hyperplasia, and presumably contributes to abnormal growth. In 10% to 20% of adenomas, overexpression occurs by a pericentromeric inversion of chromosome 11 that juxtaposes *PRAD1* with the 5'-regulatory region of the *CCND1* gene, thus directing overexpression of cyclin D1 in the parathyroid gland. The second common abnormality is the *MEN1* gene on chromosome 11q13, germ-line mutations of which are responsible for the MEN-1 syndrome. Parathyroid tumors not associated with the MEN-1 syndrome also demonstrate mutations of the *MEN1* gene.





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Figure 20-19 Technetium-99m-sestamibi radionuclide scan demonstrates an area of increased uptake corresponding to a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from hyperplastic glands. A single gland would demonstrate increased uptake.

## Morphology

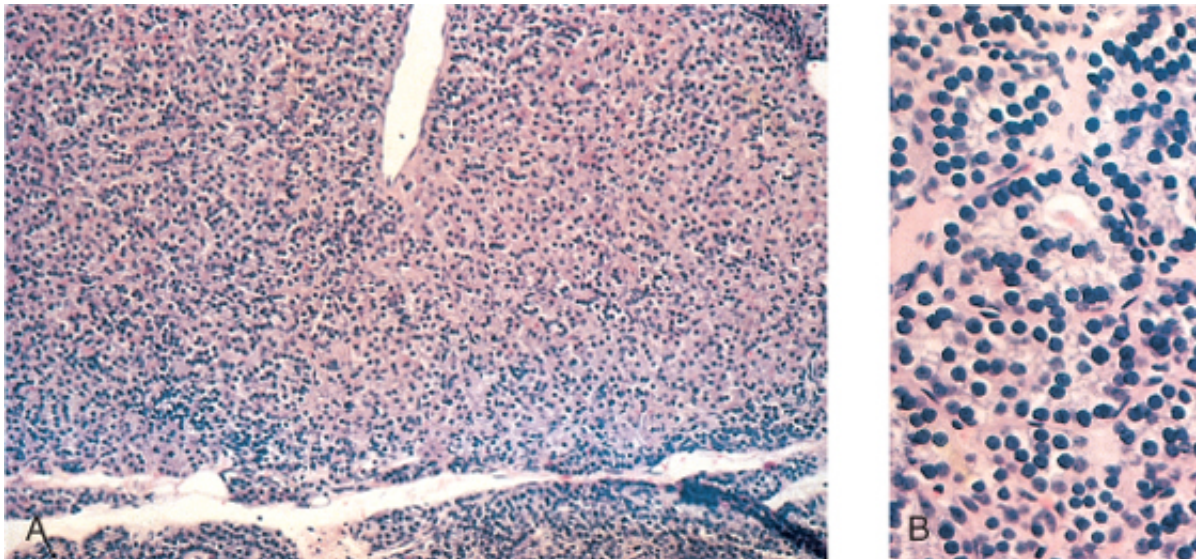
The morphologic changes seen in primary hyperparathyroidism include those in the parathyroid glands as well as those in other organs affected by elevated levels of calcium. In 75% to 80% of cases, the parathyroid glands harbor a solitary **adenoma**, which, like the normal parathyroids, may be located within the thyroid gland or in an ectopic site (e.g., the mediastinum). The typical parathyroid adenoma is a well-circumscribed, soft, tan nodule, invested by a delicate capsule. **By definition, parathyroid adenomas are almost invariably confined to single glands (Fig. 20-19)**, and the remaining glands are usually somewhat shrunk, as a result of feedback inhibition by elevations in serum calcium. Parathyroid adenomas weigh between 0.5 and 5 gm. Microscopically, parathyroid adenomas are composed predominantly of chief cells (Fig. 20-20). In most cases, at least a few nests of large, pale-staining chief cells are present. A rim of compressed, non-neoplastic parathyroid tissue, generally separated from the adenoma by a thin capsule, is often visible at the edge of the adenoma. This constitutes a helpful internal control. Parathyroid adenomas are larger and show greater nuclear size variability than the normal chief cells. The presence of bizarre and pleomorphic nuclei even within adenomas (so-called endocrine carcinoma) should not be used as a criterion for malignancy. Mitotic figures are rare. In contrast to the normal parathyroid parenchyma, adipose tissue is inconspicuous within the adenoma.

**Parathyroid hyperplasia is characteristically a multiglandular process.** In some cases, the enlargement may be grossly apparent in only one or two glands, complicating the distinction between hyperplasia and adenoma. The combined weight of all glands may exceed 1 gm but is usually less than 2 gm. Microscopically, the most common pattern seen is that of chief-cell hyperplasia, with all four glands in a diffuse or multinodular pattern. Less commonly, the constituent cells contain abundant cytoplasm due to accumulation of glycogen, a condition designated as water-clear cell hyperplasia. In cases of adenomas, stromal fat is inconspicuous within foci of hyperplasia.

**Parathyroid carcinomas** are usually firm or hard tumors, adhering to the surrounding thyroid tissue or showing fibrosis or infiltrative growth (intraoperatively, a fibrous and adherent parathyroid is suspicious for carcinoma rather than an adenoma). Parathyroid carcinomas are much larger than adenomas, almost always more than 5 gm and sometimes exceeding 10 gm. Like adenomas, parathyroid carcinomas are typically single-gland disorders, and chief cells are present in most cases. The cytologic features and mitotic activity can be quite variable, sharing features with those in adenomas; therefore, neither can be reliably used to diagnose parathyroid carcinoma. Only two valid criteria for malignancy are (1) invasion of surrounding tissues and (2) distant metastases.

**Morphologic changes in other organs** deserving special mention are found in the skeleton. **Skeletal changes** include prominence of osteoclasts, which in turn erode bone matrix, releasing calcium salts, particularly in the metaphyses of long tubular bones. Bone resorption is accompanied by increased osteoblastic activity and the formation of new bone trabeculae. In many cases the trabeculae are widely spaced, delicate trabeculae reminiscent of those seen in osteoporosis. In more advanced cases, the trabeculae are thickened and the spaces are narrowed.

widely spaced, delicate trabeculae reminiscent of those seen in osteoporosis. In the cortex is grossly thinned and the marrow contains increased amounts of fibrous tissue of hemorrhage and cyst formation (**osteitis fibrosa cystica**). Aggregates of osteoclasts and hemorrhagic debris occasionally form masses that may be mistaken for neoplasms (hyperparathyroidism). PTH-induced hypercalcemia favors the formation of urinary calculi (nephrolithiasis) as well as calcification of the renal interstitium and tubules (nephrocalcinosis). Calcification secondary to hypercalcemia may also be seen in other sites, including myocardium, and blood vessels.



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Figure 20-20 **A**, Solitary chief-cell parathyroid adenoma (*low-power view*) revealing clear delineation from the residual parathyroid tissue. There is slight variation in nuclear size and tendency to follicular formation.

### Clinical Features

Primary hyperparathyroidism is usually a disease of adults and is more common in women than in men. The *common manifestation of primary hyperparathyroidism is an increase in serum ionized calcium*. It is the most common cause of *clinically silent hypercalcemia*. It should be noted that other conditions also cause hypercalcemia. *Malignancy*, in particular, is the most common cause of *clinically apparent hypercalcemia* in adults. In individuals with malignancy-associated hypercalcemia, the response to treatment is poor, in that it more frequently occurs in persons with hypercalcemia caused by parathyroid hyperfunction, serum PTH is inappropriately elevated. In hypercalcemia caused by nonparathyroid diseases, including malignancy, PTH is undetectable. Other clinical features include hypophosphatemia and increased urinary excretion of both calcium and phosphate.

**Table 20-4. Causes of Hypercalcemia**

<b>Raised PTH</b>	<b>Decreased PTH</b>
Hyperparathyroidism	Hypercalcemia of malignancy
Primary (adenoma >hyperplasia)*	Osteolytic metastases PTH-rP mediated
Secondary†	Vitamin D toxicity
Tertiary‡	Immobilization
Familial hypocalciuric hypercalcemia	Drugs (thiazide diuretics) Granulomatous diseases (sarcoidosis)

\*Primary hyperparathyroidism is the most common cause of hypercalcemia overall. Malignancy is the most common cause of symptomatic hypercalcemia. Hyperparathyroidism and malignancy account for nearly 90% of cases of hypercalcemia.



<sup>†</sup>Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.  
PTH, parathyroid hormone; PTH-rP, PTH-related protein.

Primary hyperparathyroidism has been traditionally associated with a constellation of symptoms the "abdominal groans, and psychic moans". Pain, secondary to fractures of bones weakened by osteoporosis, resulting from renal stones, with obstructive uropathy, was at one time a prominent manifestation of the disease. Serum calcium is now routinely assessed in the work-up of most patients who need blood tests for hyperparathyroidism is detected early. Hence, many of the classic clinical manifestations, particularly the "abdominal groans," are seen much less frequently. Additional signs and symptoms that may be encountered are the following:

*Gastrointestinal disturbances*, including constipation, nausea, peptic ulcers, pancreatitis, and weight loss; *Neuromuscular abnormalities*, including depression, lethargy, and seizures; *Renal alterations*, including polyuria and muscle weakness, are clearly related to the disease. Many of the other manifestations of the disorder remain poorly understood.

Although some of these alterations, for example, polyuria and muscle weakness, are clearly related to the disease, many of the other manifestations of the disorder remain poorly understood.

### Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by any condition associated with a chronic depression of serum calcium levels. The hypocalcemia leads to compensatory overactivity of the parathyroids. *Renal failure is by far the most common cause of secondary hyperparathyroidism.* The mechanisms by which chronic renal failure induces secondary hyperparathyroidism are poorly understood. Chronic renal insufficiency is associated with decreased phosphate excretion, which elevates serum phosphate levels. Elevated serum phosphate levels directly depress serum calcium levels and thereby stimulate parathyroid secretion. Parathyroid hormone (PTH) reduces the availability of  $\alpha_1$ -hydroxylase necessary for the synthesis of the active form of vitamin D, which reduces intestinal absorption of calcium (Chapter 8).

#### Morphology

**The parathyroid glands in secondary hyperparathyroidism are hyperplastic.** In secondary hyperparathyroidism, the degree of glandular enlargement is not necessarily symmetric. Microscopically, hyperplastic glands contain an increased number of chief cells, or cells with more abundant cytoplasm (water-clear cells), in a diffuse or multinodular distribution. Fat cells are decreased. The histologic changes similar to those seen in primary hyperparathyroidism may also be present. These changes may be seen in many tissues, including lungs, heart, stomach, and blood vessels.

#### Clinical Features

The clinical manifestations of secondary hyperparathyroidism are usually dominated by those related to the renal abnormalities (*renal osteodystrophy*) and other changes associated with PTH excess are, in general, similar to those seen in primary hyperparathyroidism. Serum calcium remains near normal because the compensatory increase in PTH secretion maintains calcium levels. The metastatic calcification of blood vessels (secondary to hyperphosphatemia) may occur. Damage to skin and other organs, a process sometimes referred to as *calciophylaxis*. In a minority of cases, the hyperplastic parathyroid glands become autonomous and excessive, with resultant hypercalcemia, a process sometimes termed *tertiary hyperparathyroidism*. Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients.

### SUMMARY

**Hyperparathyroidism** Primary hyperparathyroidism is the most common cause of hypercalcemia. In the majority of cases, primary hyperparathyroidism is caused by a parathyroid adenoma, and, less commonly, by parathyroid hyperplasia. Parathyroid adenoma is typically a solitary, while hyperplasia is typically a multiglandular process. Skeletal manifestations of primary hyperparathyroidism include bone resorption, *osteitis fibrosa cystica*, and "brown tumor" changes. Renal changes include nephrolithiasis (stones) and nephrocalcinosis. The clinical manifestations of primary hyperparathyroidism can be summarized as "painful bones, renal stones, abdominal groans, and psychic moans." Secondary hyperparathyroidism is most often caused by renal failure. The parathyroid glands are hyperplastic. Malignancies are the most important cause of hypercalcemia, which results from osteolytic metastases or release of PTH-related protein.

parathyroid tumors.



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## HYPOPARATHYROIDISM

Hypoparathyroidism is far less common than is hyperparathyroidism. The major causes of hypoparathyroidism include the following:

*Surgical ablation:* inadvertent removal of parathyroids during thyroidectomy. *Congenital absence:* usually occurs in conjunction with thymic aplasia and cardiac defects in DiGeorge syndrome ([Chapters 5](#) and [7](#)). *Autoimmune hypoparathyroidism:* a hereditary polyglandular deficiency syndrome arising from autoantibodies to multiple endocrine organs (parathyroid, thyroid, adrenals, and pancreas). Chronic fungal infections involving the skin and mucous membranes (mucocutaneous candidiasis) are sometimes encountered in these individuals, suggesting an underlying defect in T-cell function. This condition is discussed more extensively in the context of autoimmune adrenalitis.

The major clinical manifestations of hypoparathyroidism are referable to hypocalcemia and include *increased neuromuscular irritability (tingling, muscle spasms, facial grimacing, and sustained carpopedal spasm or tetany)*, cardiac arrhythmias, and, on occasion, *increased intracranial pressures and seizures*. Morphologic changes are generally inconspicuous but may include cataracts, calcification of the cerebral basal ganglia, and dental abnormalities.





## ENDOCRINE PANCREAS

The endocrine pancreas consists of about 1 million microscopic clusters of cells, the islets of Langerhans, which contain four major cell types- $\beta$ ,  $\alpha$ ,  $\delta$ , and PP (pancreatic polypeptide) cells. The cells can be differentiated morphologically by their staining properties, by the ultrastructural structure of their granules, and by their hormone content. *The  $\beta$  cell produces insulin*, which is the most potent anabolic hormone known, with multiple synthetic and growth-promoting effects; *the  $\alpha$  cell secretes glucagon*, inducing hyperglycemia by its glycogenolytic activity in the liver;  *$\delta$  cells contain somatostatin*, which suppresses both insulin and glucagon release; and *PP cells contain a unique pancreatic polypeptide* (vasoactive intestinal peptide, VIP) that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility.







## DIABETES MELLITUS

Diabetes mellitus is not a single disease entity but rather a *group of metabolic disorders sharing the hyperglycemia*. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, hyperglycemia and attendant metabolic dysregulation of diabetes mellitus may be associated with systems, especially the kidneys, eyes, nerves, and blood vessels. Diabetes affects an estimated 2 (nearly 7% of the population), as many as a third of whom are undiagnosed. Diabetes is a leading onset blindness, and nontraumatic lower extremity amputations in the United States, underscoring of health care costs. It also greatly increases the risk of developing coronary artery disease and cardiovascular disease. Despite great technologic advances, there have been pronounced changes in human behavior, with increased eating habits. This has contributed to the simultaneous escalation of diabetes and obesity worldwide "diabetes" epidemic.

### Diagnosis

Blood [glucose](#) levels are normally maintained in a very narrow range, usually 70 to 120 mg/dL. Diabetes is diagnosed by elevation of blood [glucose](#) by any one of three criteria:

1. A random blood [glucose](#) concentration of 200 mg/dL or higher, with classical signs and symptoms.
2. A fasting [glucose](#) concentration of 126 mg/dL or higher on more than one occasion, or
3. An abnormal oral [glucose](#) tolerance test (OGTT), in which the [glucose](#) concentration is  $\geq 200$  mg/dL 2 hours after a standard carbohydrate load (75 gm of [glucose](#)).

Derangements in carbohydrate metabolism proceed along a continuum. Individuals with serum fasting glucose  $\geq 126$  mg/dL, or less than 140 mg/dL following an OGTT, are considered to be euglycemic. However, those with fasting glucose  $\geq 110$  but less than 126 mg/dL, or OGTT values of greater than 140 but less than 200 mg/dL, are considered to have *impaired glucose tolerance*. Individuals with impaired [glucose](#) tolerance have a significant risk of progressing to overt diabetes. Approximately 5% to 10% advancing to full-fledged diabetes mellitus per year. In addition, those with impaired [glucose](#) tolerance and *cardiovascular disease*, due to abnormal carbohydrate metabolism and the coexistence of other risk factors, are at a higher risk for cardiovascular morbidity and mortality.

### Classification

Although all forms of diabetes mellitus share hyperglycemia as a common feature, the underlying pathogenesis is different. *The vast majority of cases of diabetes fall into one of two broad classes:*

*Type 1 diabetes* is characterized by an absolute deficiency of insulin secretion caused by autoimmune destruction of the pancreatic  $\beta$  cells, resulting from an autoimmune attack. Type 1 diabetes accounts for approximately 10% of all cases of diabetes. *Type 2 diabetes* is characterized by a combination of peripheral resistance to insulin action and an inadequate compensatory response of the pancreatic  $\beta$  cells ("relative insulin deficiency"). Approximately 80% to 90% of patients have type 2 diabetes.

A variety of monogenic and secondary causes make up the remaining cases of diabetes ([Table 20-2](#)). The major types of diabetes have different pathogenic mechanisms, *the long-term complications in children and adults are the same and are the principal causes of morbidity and death*.

### Normal Insulin Physiology and [Glucose](#) Homeostasis

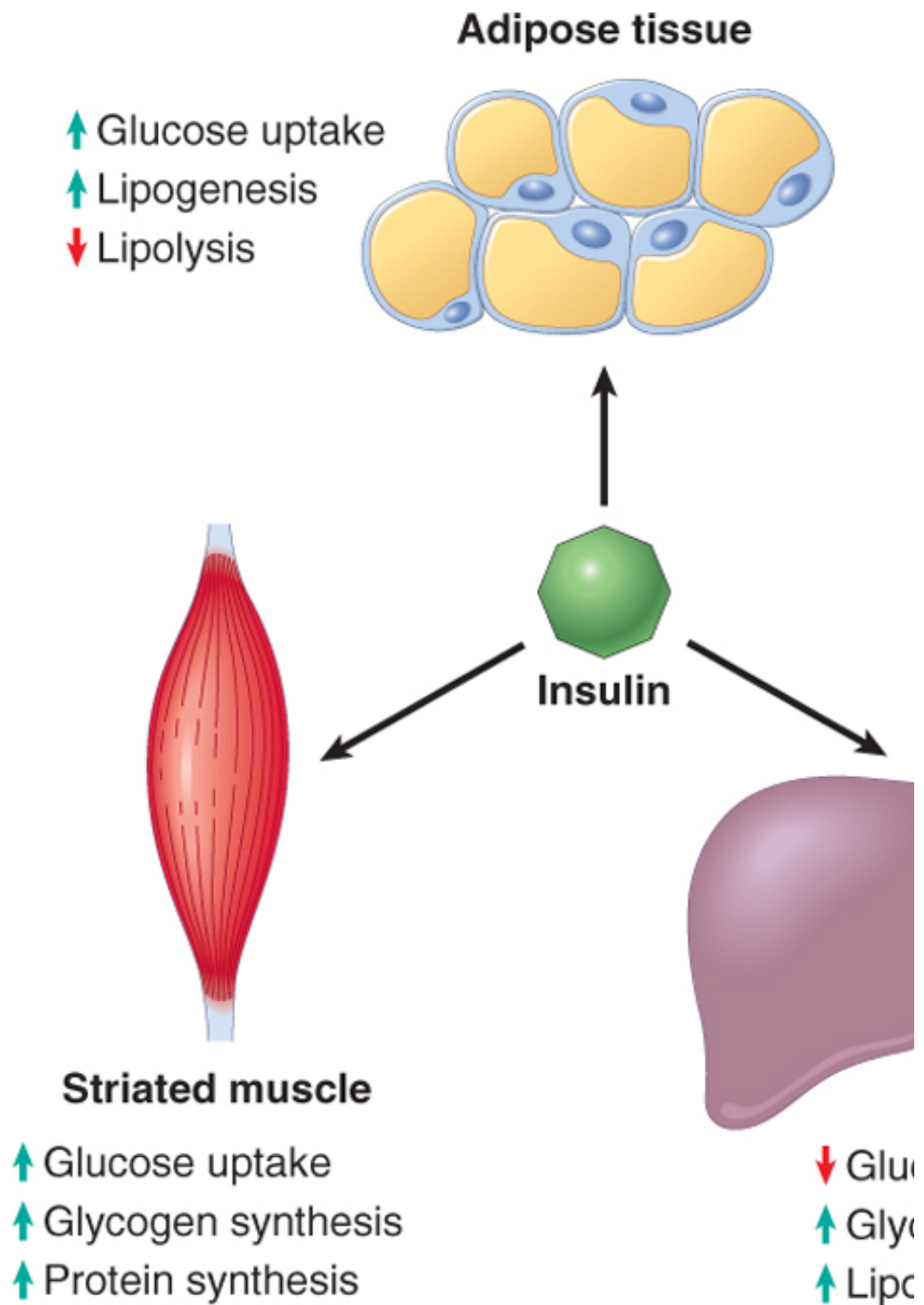
Before discussing the pathogenesis of the two major types of diabetes, we briefly review normal insulin physiology and [glucose](#) homeostasis. *Normal [glucose](#) homeostasis is tightly regulated by three interrelated processes:* (1) [glucose](#) uptake and utilization by peripheral tissues, chiefly skeletal muscle, and, (2) actions of insulin (e.g., glucagon). *The principal metabolic function of insulin is to increase the rate of [glucose](#) transport into cells (e.g., striated muscle cells (including myocardial cells) and, to a lesser extent, adipocytes, which constitute two-thirds of the entire body weight. [Glucose](#) uptake in other peripheral tissues, most notably the liver, is also regulated by insulin.*

two-thirds of the entire body weight. **Glucose<sup>R</sup>** uptake in other peripheral tissues, most notably the cells, **glucose<sup>R</sup>** is then either stored as glycogen or oxidized to generate **adenosine<sup>R</sup>** triphosphate primarily stored as lipid. Besides promoting lipid synthesis (lipogenesis), insulin also inhibits lipid c Similarly, insulin promotes amino acid uptake and protein synthesis while inhibiting protein degrad *insulin can be summarized as anabolic, with increased synthesis and reduced degradation of glyc* these metabolic effects, insulin has several *mitogenic* functions, including initiation of DNA synthe growth and differentiation.

**Table 20-5. Etiologic Classification of Diabetes Mellitus**

<b>1. Type 1 Diabetes</b>
β-cell destruction, leads to absolute insulin deficiency
<b>2. Type 2 Diabetes</b>
Insulin resistance with relative insulin deficiency
<b>3. Genetic Defects of β-Cell Function</b>
MODY, caused by mutations in:
HNF-4α(MODY1)
Glucokinase (MODY2)
HNF-1α(MODY3)
IPF-1 (MODY4)
HNF-1β(MODY5)
Neuro D1 (MODY6)
Mitochondrial DNA mutations
<b>4. Genetic Defects in Insulin Processing or Insulin Action</b>
Defects in proinsulin conversion
Insulin gene mutations
Insulin receptor mutations
<b>5. Exocrine Pancreatic Defects</b>
Chronic pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy
<b>6. Endocrinopathies</b>
Growth hormone excess (acromegaly)
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
<b>7. Infections</b>
Cytomegalovirus
Coxsackievirus B
<b>8. Drugs</b>
Glucocorticoids
Thyroid hormone
β-adrenergic agonists
<b>9. Genetic Syndromes Associated with Diabetes</b>
Down syndrome
Klinefelter syndrome

HNF, hepatocyte nuclear factor; IPF-1, insulin promoter factor 1; MODY, maturity-onset diabetes of the young; Neuro D1, neuroger  
Adapted from the Report of the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Dia  
S20, 2002.



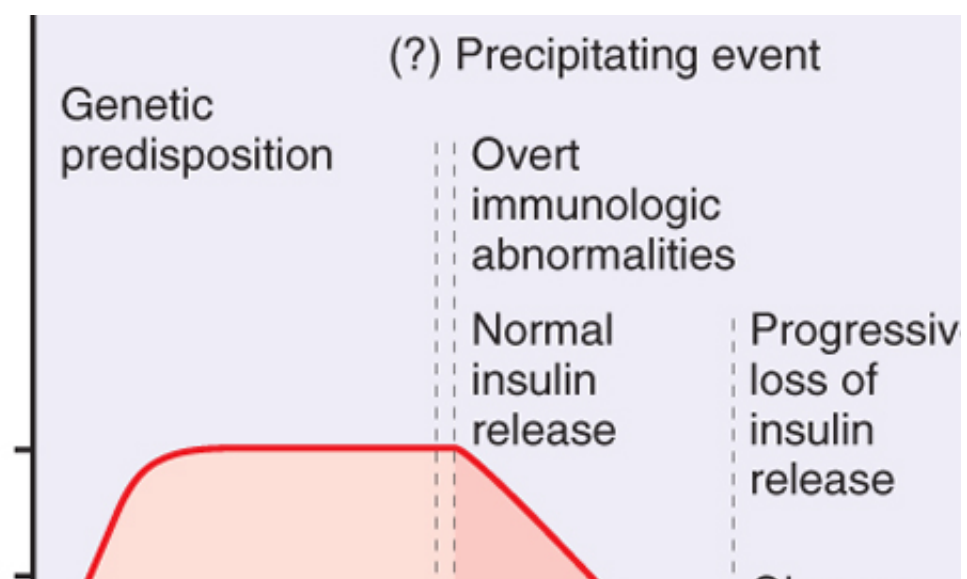
Insulin reduces the production of *glucose*<sub>R</sub> from the liver. Insulin and glucagon have opposing reg During *fasting* states, low insulin and high glucagon levels facilitate hepatic gluconeogenesis and while decreasing glycogen synthesis, thereby preventing hypoglycemia. Thus, *fasting* plasma *gluc* hepatic *glucose*<sub>R</sub> output. Following a meal, insulin levels rise and glucagon levels fall in response *important stimulus that triggers insulin release is glucose*<sub>R</sub> itself, which initiates insulin synthesis i including intestinal hormones and certain *amino acids*<sub>R</sub> (leucine and arginine), stimulate insulin re tissues (skeletal muscle and adipose tissue), secreted insulin binds to the *insulin receptor*, trigger that promote *glucose*<sub>R</sub> uptake and post-prandial *glucose*<sub>R</sub> utilization, thereby maintaining *glucose* points along this complex signaling cascade, from synthesis and release of insulin by  $\beta$  cells to ins tissues, can result in the diabetic phenotype.

### Pathogenesis of Type 1 Diabetes Mellitus

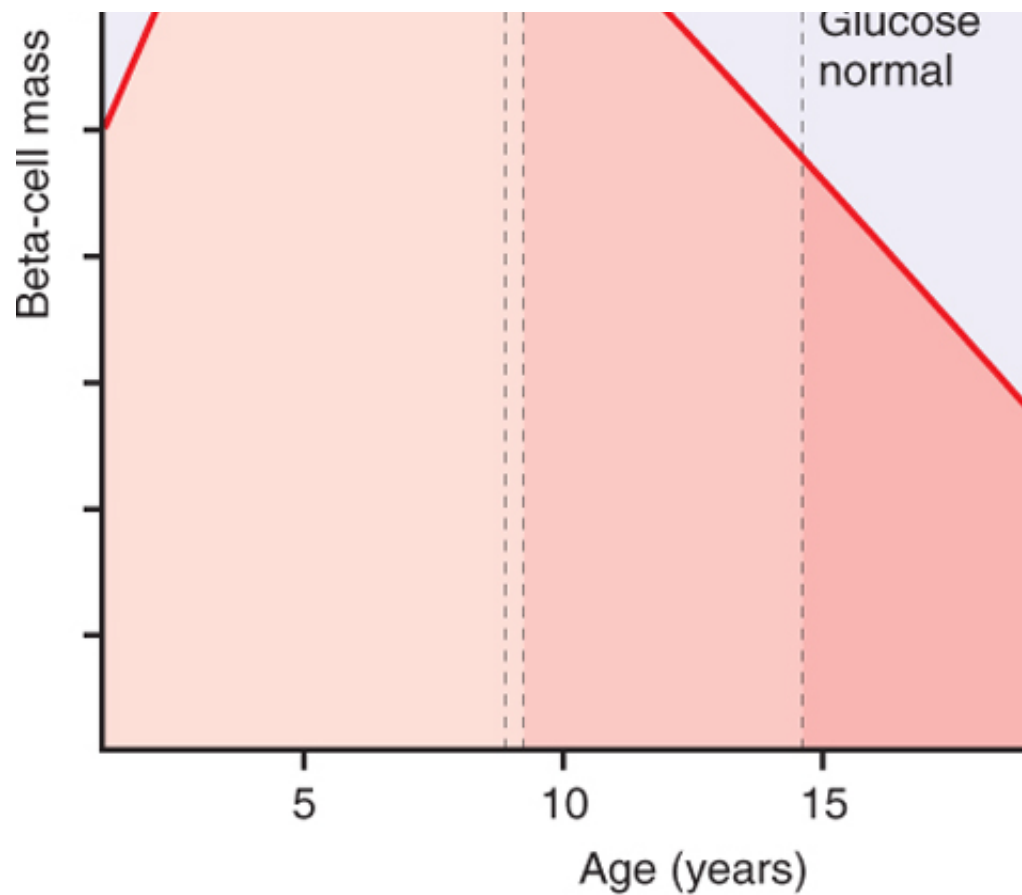
Type 1 diabetes is an *autoimmune disease* in which islet destruction is caused primarily by T lymph defined  $\beta$ -cell antigens, resulting in a reduction in  $\beta$ -cell mass. Recent studies have implicated imr itself as a target antigen for autoimmune injury, but it remains to be convincingly established whet cases of type 1 diabetes or in only a subset. What is also unclear is how immunologic tolerance b diabetes. As in all autoimmune diseases, genetic susceptibility and environmental influences play Type 1 diabetes most commonly develops in childhood, becomes manifest at puberty, and is prog type 1 diabetes depend on exogenous insulin supplementation for survival, and without insulin, th complications such as acute ketoacidosis and coma.

Although the clinical onset of type 1 diabetes is abrupt, this disease in fact results from a chronic ; starts many years before the disease becomes evident (Fig. 20-22). The classic manifestations of occur late in its course, after more than 90% of the  $\beta$  cells have been destroyed. *Several mechan* it is likely that many of these immune mechanisms work together to produce progressive loss of  $\beta$

*T lymphocytes* react against  $\beta$ -cell antigens and cause cell damage. These T cells include cause tissue injury by activating macrophages, and CD8+ cytotoxic T lymphocytes, which ( cytokines that activate macrophages. In the rare cases in which the pancreatic lesions hav stages of the disease, the islets show cellular necrosis and lymphocytic infiltration. This les *cytokines* damage  $\beta$  cells. Among the cytokines implicated in the cell injury are IFN- $\gamma$ , prod factor and interleukin-1, produced by macrophages that are activated during the immune re of  $\beta$ -cell antigens, including insulin and glutamic acid decarboxylase, are also detected in tl may contribute to islet damage.







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 Figure 20-22 Stages in the development of type 1 diabetes mellitus. The stages are listed from left to right, and I  
 (From Eisenbarth GE: Type 1 diabetes-a chronic autoimmune disease. N Engl J Med

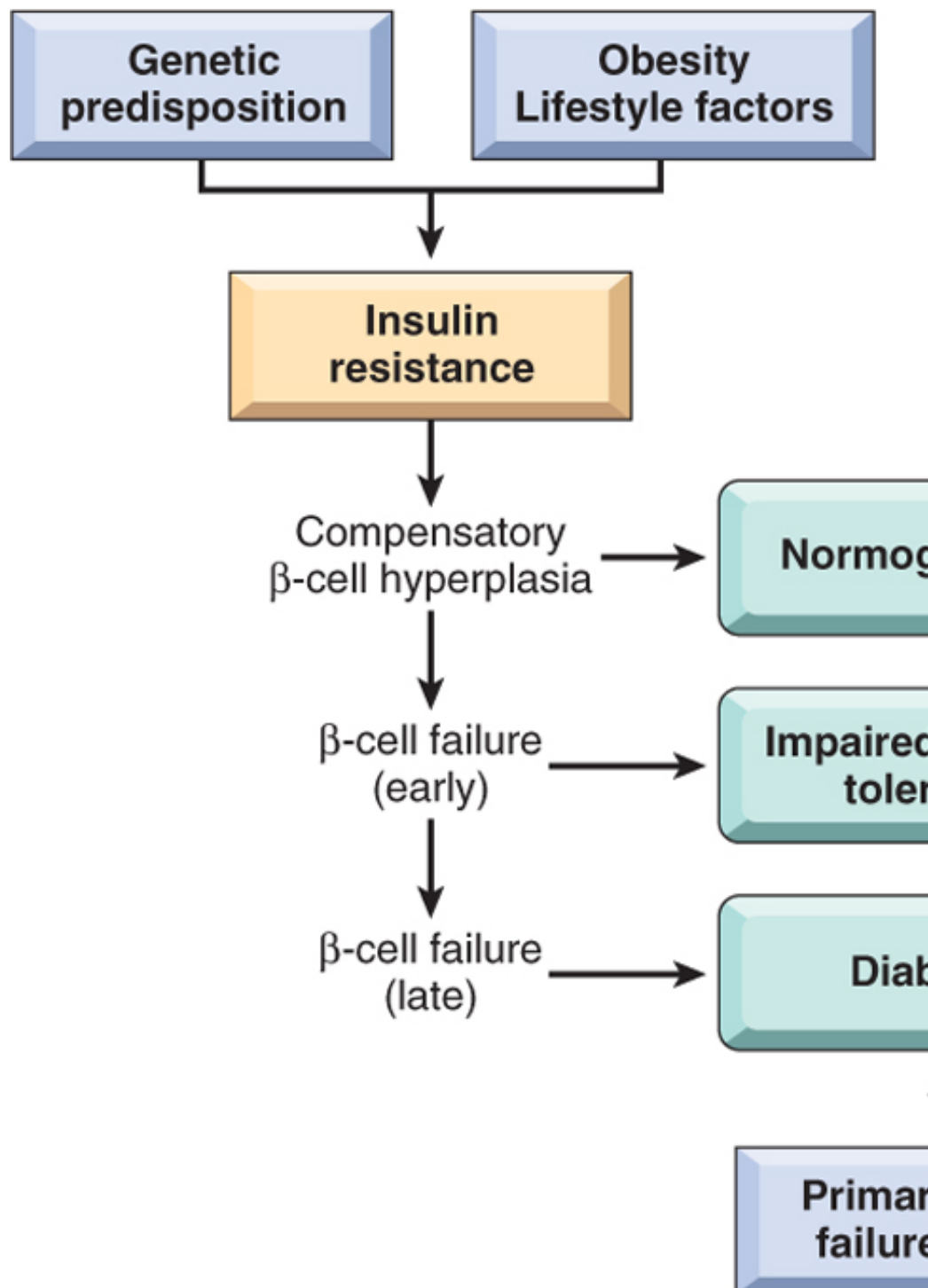
Type 1 diabetes has a *complex pattern of genetic association*, and putative susceptibility genes have been identified in several chromosomal regions. Of these, *the principal susceptibility locus for type 1 diabetes resides in the region of the major histocompatibility complex (MHC) on chromosome 6p21 (HLA-D)*. Between 90% and 95% of Caucasians with type 1 diabetes have the DR3/DR4 heterozygote genotype, in contrast to about 40% of normal subjects, and 40% to 50% of patients are DR3/DR4 heterozygotes. Despite the high relative risk of type 1 diabetes in individuals with particular class II alleles, most do not develop the disease. Another gene shown to be weakly associated with the disease encodes the protein tyrosine phosphatase (PTPase). Individuals with type 1 diabetes show increased frequency of a splice variant that may abrogate the ability of PTPase to keep self-reactive T lymphocytes under control. As mentioned above, we do not know the actual genes involved. There is also evidence to suggest that *environmental factors*, especially infections, may be involved in the pathogenesis of autoimmune diseases. It has been proposed that viruses may be an initiating trigger, perhaps because of their antigenic similarity to  $\beta$  cell antigens (molecular mimicry), but this idea is unproved. The controversy surrounding the role of infections is actually protective.

### Pathogenesis of Type 2 Diabetes Mellitus

While much has been learned in recent years, the pathogenesis of type 2 diabetes remains enigmatic. Sedentary life style and dietary habits, clearly have a role, as will become evident when obesity is more prevalent. *are even more important than in type 1 diabetes*, with linkage demonstrable to multiple "diabetogenic" genes. The concordance rate is 50% to 90%, while among first-degree relatives with type 2 diabetes (including those with the disease) is 20% to 40%, as compared with 5% to 7% in the population at large. Unlike type 1 diabetes, type 2 is not linked to genes involved in immune tolerance and regulation, and there is no evidence to suggest that it is an autoimmune disease. *The two metabolic defects that characterize type 2 diabetes are (1) a decreased ability of peripheral tissues to utilize glucose (insulin resistance) and (2)  $\beta$ -cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance.*

(Fig. 20-23). In most cases, insulin resistance is the primary event and is followed by increasing d

### **Insulin Resistance**



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Figure 20-23 Pathogenesis of type 2 diabetes mellitus. Genetic predisposition and environmental influences converge to cause insulin resistance. Insulin resistance can be compensated for by  $\beta$ -cell hyperplasia, which can maintain normoglycemia, but eventually  $\beta$ -cell secretory dysfunction sets in, leading to impaired glucose tolerance and eventually diabetes. Rare instances of primary  $\beta$ -cell failure can directly lead to type 2 diabetes without insulin resistance.

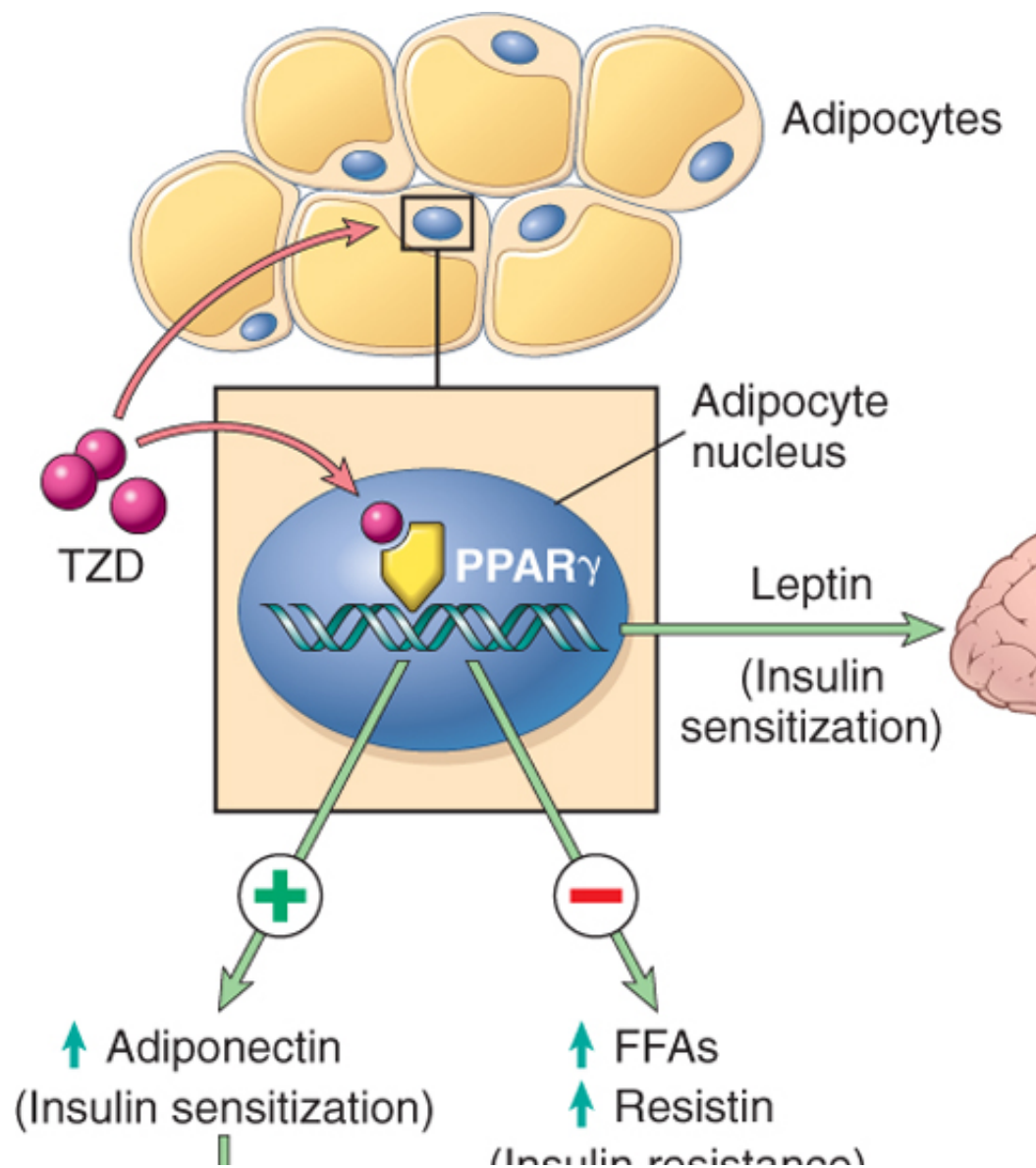
Insulin resistance is defined as resistance to the effects of insulin on glucose uptake, metabolism

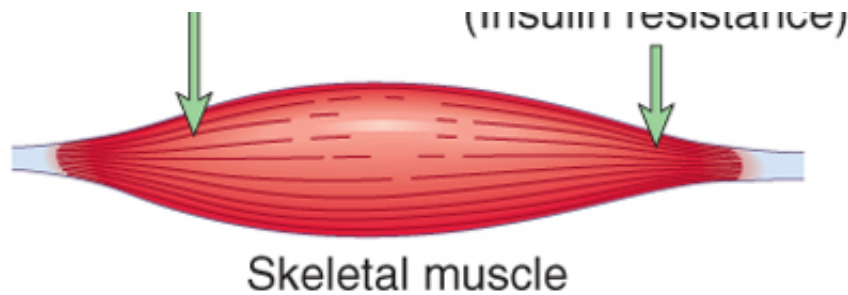
characteristic feature of most individuals with type 2 diabetes and is an almost universal finding in evidence that insulin resistance has a major role in the pathogenesis of type 2 diabetes can be ga resistance is often detected 10 to 20 years before the onset of diabetes in predisposed individuals (2) in prospective studies, insulin resistance is the best predictor for subsequent progression to di resistance is a complex phenomenon, influenced by a variety of genetic and environmental factor.

#### Genetic Defects of the Insulin Receptor and Insulin Signaling Pathway

Loss-of-function abnormalities of either the insulin receptor or its down-stream signaling molecule insulin resistance in type 2 diabetes. Much of the role of genetic defects in the insulin signaling pa disruption of these genes in knockout mouse models of diabetes. Unfortunately, the extrapolation human disease has been less than gratifying, underscoring the *multifactorial etiology of insulin re*: the insulin receptor are relatively rare, accounting for no more than 1% to 5% of patients with insu Diabetes"). The vast majority of individuals with conventional type 2 diabetes, however, do *not* ha insulin receptor or other components of the insulin-signaling pathway.

#### Obesity and Insulin Resistance





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Figure 20-24 Obesity and insulin resistance: the missing links? Adipocytes release a variety of factors (free fatty acids) that play a role in modulating insulin resistance in peripheral tissues (illustrated here is striated muscle). Excess FFAs and, in contrast, adiponectin, whose levels are decreased in obesity, is an insulin-sensitizing adipocytokine. Leptin is also released by adipocytes and acts on its receptors (in the hypothalamus). The peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is a nuclear receptor expressed in adipocytes. Sensitizing drugs called thiazolidinediones (TZDs). The mechanism of action of TZDs may eventually be mediated through the same intracellular signaling pathways that favor a state of insulin sensitivity.

The association of obesity with type 2 diabetes has been recognized for decades, with visceral obesity being a major risk factor for type 2 diabetes. Insulin resistance is *the link between obesity and diabetes* (Fig. 20-24). The risk of developing type 2 diabetes increases with increasing body mass index (a measure of body fat content), suggesting a dose-response relationship between obesity and type 2 diabetes. Although many details of the "adipo-insulin axis" remain to be elucidated, there has been a substantial amount of research into the putative pathways leading to insulin resistance:

**Role of free fatty acids (FFAs):** Cross-sectional studies have demonstrated an inverse correlation between obesity and insulin sensitivity. The level of intracellular triglycerides is often markedly increased in muscle, presumably because excess circulating FFAs are deposited in these organs. Intracellular triglycerides and FFAs are potent inhibitors of insulin signaling and result in an acquired insulin resistance. FFAs are most likely mediated through a decrease in activity of key insulin-signaling proteins. **Adipose tissue:** Adipose tissue is not merely a passive storage depot for fat; it can operate as an endocrine organ, secreting hormones in response to extracellular stimuli or changes in the metabolic status. A variety of hormones secreted by adipose tissue have been identified, and these are collectively termed *adipocytokines*. **Adiponectin** and **resistin**; changes in their levels are associated with insulin resistance. For example, adiponectin levels are decreased in obesity and insulin resistance, suggesting that, under physiologic conditions, this hormone promotes insulin sensitivity in peripheral tissues. Conversely, levels of resistin are increased in obesity and insulin resistance. **Role of the PPAR $\gamma$  and thiazolidinediones (TZD):** TZDs are a class of antidiabetic drugs developed in the early 1980s as antioxidants. The target receptor for TZDs has been identified as PPAR $\gamma$ . PPAR $\gamma$  is most highly expressed in adipose tissue, and its activation by TZDs results in increased adipogenesis, eventually leading to reduction of insulin resistance. The targets of PPAR $\gamma$  activation include adipocytokines discussed above. PPAR $\gamma$  activation also decreases concentrations of FFAs, contributing to insulin resistance in obesity. A family of proteins called *sirtuins*, which were first identified in yeast, have also been implicated in diabetes. The best-studied mammalian sirtuin, called Sirt-1, has been shown to enhance  $\beta$  cell insulin secretion, and increase production of adiponectin. It remains to be seen whether sirtuins play a role in the pathogenesis of type 2 diabetes.

To summarize, insulin resistance in type 2 diabetes is a complex and multifactorial phenomenon. The specific genetic pathway are not common, and when present, they are more likely to be subtle variations in function rather than a single profound inactivating mutation. Insulin resistance is present in the overwhelming majority of type 2 diabetics, and is central to this phenomenon (see Fig. 20-24). Several possible links between obesity and insulin resistance have been proposed, including excessive amounts of FFAs and a variety of adipocyte-specific products (adipocytokines). TZDs act on the PPAR $\gamma$  receptor, and represent one of the many major advances achieved in ameliorating insulin resistance.

### **$\beta$ -Cell Dysfunction**

$\beta$ -cell dysfunction in type 2 diabetes reflects the inability of these cells to adapt themselves to the increasing insulin resistance and increased insulin secretion. In states of insulin resistance, insulin secretion is initially normal, but eventually declines.



in controls. This hyperinsulinemic state is a compensation for peripheral resistance and can often persist for years. Although the data in humans are scant, studies from animal models of diabetes support the idea that  $\beta$ -cell hyperplasia in the pre-diabetic state is followed by decrease in  $\beta$ -cell mass that coincides with the onset of diabetes. Eventually, however,  $\beta$ -cell compensation becomes inadequate, and there is progressive loss of  $\beta$ -cell mass. The mechanism for failure of  $\beta$ -cell adaptation is not known, although it is postulated that several mechanisms, including free fatty acids ("lipotoxicity") or chronic hyperglycemia ("glucotoxicity"), may have a role.  *$\beta$ -cell dysfunction involves both qualitative and quantitative aspects.*

Qualitative  $\beta$ -cell dysfunction is initially manifest as subtle abnormalities, such as loss in the first phase of insulin secretion, and attenuation of the rapid first phase of insulin secretion triggered by elevated glucose. As the secretory defect progresses to encompass all phases of insulin secretion, and even the second phase, compensation becomes inadequate for overcoming insulin resistance. Quantitative  $\beta$ -cell dysfunction involves *loss of  $\beta$ -cell mass, islet degeneration, and deposition of islet amyloid*. Islet amyloid protein (amylin) is co-secreted with insulin by  $\beta$ -cells in type 2 diabetes, and it is present in more than 90% of diabetic islets examined. Islet amyloid deposition leads to a loss of  $\beta$ -cell mass, although it is uncertain whether the amyloid is a cause or consequence of  $\beta$ -cell dysfunction. In this context, it is important to note that even a "normal"  $\beta$ -cell mass in diabetic individuals may be inadequate, compared with the expected hyperplasia needed to compensate for insulin resistance.

### Monogenic Forms of Diabetes

Types 1 and 2 diabetes are genetically complex, and despite the associations with multiple susceptibility loci, a single mutation can account for predisposition to these entities. In contrast, monogenic forms of diabetes are caused by a single mutation in a single gene. These forms of diabetes are either a primary defect in  $\beta$ -cell function or a defect in insulin-insulin receptor signaling.

### Pathogenesis of the Complications of Diabetes

Most of the available experimental and clinical evidence suggests that the complications of diabetes are caused by chronic hyperglycemia. At least three distinct metabolic pathways seem to be involved in the pathogenesis of diabetic complications, although the primacy of any one has not been established. These pathways are:

1. *Non-enzymatic glycosylation*. This is the process by which glucose chemically attaches to free amino groups on proteins and lipids without the aid of enzymes. The degree of nonenzymatic glycosylation is directly related to blood glucose level; hemoglobin levels in blood is useful in the management of diabetes mellitus, because it provides a measure of average glucose levels over the 120-day life span of erythrocytes. The early glycosylation products of collagen and other extracellular matrix proteins and blood vessel walls undergo a slow series of chemical rearrangements to form irreversible cross-links (AGEs), which accumulate over the lifetime of the vessel wall. AGEs have a number of chemical and biologic effects that are pathogenic to extracellular matrix components and to the target cells of diabetic complications:

AGE formation on proteins such as collagen causes cross-links between polypeptides; this in turn leads to stiffening of the extracellular matrix and interstitial proteins. In large vessels, trapping low-density lipoprotein, for example, retards the clearance of cholesterol in the intima, thus accelerating atherosclerosis. In the glomeruli, plasma proteins such as albumin bind to the glycated basement membrane, accelerating the process of glomerular basement membrane thickening characteristic of diabetic glomerulopathy. Circulating plasma proteins with AGE residues; these proteins, in turn, bind to AGE receptors on several cell types (endothelial cells, macrophages, etc.). The biologic effects of AGE-receptor signaling include (1) release of cytokines and growth factors, (2) increased endothelial permeability; (3) increased procoagulant activity on endothelial cells; (4) enhanced proliferation and synthesis of extracellular matrix by fibroblasts and smooth muscle cells. These effects contribute to diabetic complications.

2. *Activation of protein kinase C*. Activation of intracellular protein kinase C (PKC) by calcium ions and diacylglycerol (DAG) is an important signal transduction pathway in many cellular systems. Intracellular production of DAG from glycolytic intermediates and hence cause activation of PKC. The downstream effects of PKC activation are numerous and include production of *pro-angiogenic molecules* such as vascular endothelial growth factor, leading to neovascularization seen in diabetic retinopathy, and pro-fibrogenic molecules like transforming growth factor- $\beta$ , leading to deposition of extracellular matrix and basement membrane material.

deposition of extracellular matrix and basement membrane material.

3. *Intracellular hyperglycemia with disturbances in polyol pathways.* In some tissues that do not regenerate (e.g., nerves, lens, kidneys, blood vessels), hyperglycemia leads to an increase in intracellular glucose. Glucose is converted by aldose reductase to sorbitol, a polyol, and eventually to fructose. While accumulated sorbitol is implicated in causing cell injury via increased intracellular osmolarity and water influx, accumulative consequences of the aldose reductase pathway arise primarily by an increase in cellular susceptibility. Intracellular antioxidant reserves are diminished in the course of sorbitol metabolism. The importance is not clear because clinical trials using an aldose reductase inhibitor fail to significantly ameliorate

## SUMMARY

**Pathogenesis of Diabetes Mellitus and Its Long-Term Complications** Type 1 diabetes is an autoimmune disease characterized by progressive destruction of islet  $\beta$  cells, resulting in insulin deficiency. Several immune mechanisms probably contribute to  $\beta$ -cell destruction, including cytokines, and autoantibodies. Type 2 diabetes has no autoimmune basis. Central to its pathogenesis are insulin resistance and  $\beta$ -cell dysfunction, resulting in relative insulin deficiency. Obesity has an important relationship with insulin resistance (and is probably mediated by cytokines released from adipose tissues (adipocytokines)). Factors in the "adipo-insulin axis" include free fatty acids (which may cause "lipotoxicity") and leptin, which modulates adipocytokine levels. Monogenic forms of diabetes are caused by single-gene defects that result in primary  $\beta$ -cell dysfunction (e.g., *glucokinase* mutations) or abnormalities of insulin-insulin receptor signaling (e.g., insulin receptor gene mutations). The complications of diabetes are similar in both types and involve three underlying mechanisms: formation of AGEs through nonenzymatic glycosylation, activation of PKC, and increased intracellular sorbitol.

## Morphology of Diabetes and Its Late Complications

Pathologic findings in the pancreas are variable and not necessarily dramatic. The changes are related to the many late systemic complications of diabetes. There is considerable variation in the time of onset of these complications, their severity, and the particular complications involved. In individuals with tight control of diabetes the onset may be delayed. In general, morphologic changes are likely to be found in arteries (**macrovascular disease**), in small vessels (**microangiopathy**), kidneys (**diabetic nephropathy**), retina (**retinopathy**), and other tissues. These changes are seen in both type 1 and type 2 diabetes.

**Pancreas.** Lesions in the pancreas are inconstant and rarely of diagnostic value. They are more commonly associated with type 1 than with type 2 diabetes. One or more of the following may be present.

**Reduction in the number and size of islets.** This is most often seen in type 1 diabetes with rapidly advancing disease. Most of the islets are small, inconspicuous, and difficult to detect. **Leukocytic infiltration of the islets** (insulitis) principally composed of lymphocytes, is characteristic of type 1 diabetes (Fig. 20-26A). This may be present at the time of clinical presentation. The distribution of insulitis may be strikingly focal. Infiltrates may also be found, particularly in diabetic infants who fail to survive the neonatal period. **In type 2 diabetes there may be a subtle reduction in islet cell mass.** This is apparent in special morphometric studies. **Amyloid replacement of islets in long-standing diabetes.** Amyloid appears as deposition of pink, amorphous material beginning in and around the islets. At advanced stages the islets may be virtually obliterated (Fig. 20-26E). This change is often seen in long-standing cases of type 2 diabetes. It is also found in elderly nondiabetics, apparently as part of normal aging. **An increase in the size of islets is especially characteristic of nondiabetic newborns of diabetic mothers.** Presumably, fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

**Diabetic Macrovascular Disease.** Diabetes exacts a heavy toll on the vascular system. Diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large sized arteries. Except for its greater severity and earlier age of onset, atherosclerosis is indistinguishable from that in nondiabetics ([Chapter 10](#)). Myocardial infarction, caused by the coronary arteries, is the most common cause of death in diabetics. Significantly more in diabetic women as in diabetic men. In contrast, myocardial infarction is uncommon in the young of reproductive age. Gangrene of the lower extremities, as a result of advanced vascular disease, is 100 times more common in diabetics than in the general population. The larger vessels are more resistant to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is on the glomeruli and the microcirculation. This is discussed later.

**Hyaline arteriolosclerosis**, the vascular lesion associated with hypertension ([Chapter 10](#)), is more prevalent and more severe in diabetics than in nondiabetics, but it is not specifically seen in elderly nondiabetics without hypertension. It takes the form of an amorphous eosinophilic material on the wall of the arterioles, which causes narrowing of the lumen ([Fig. 20-27](#)). Not so related not only to the duration of the disease but also to the level of blood pressure.

**Diabetic Microangiopathy.** One of the most consistent morphologic features of diabetic microangiopathy is **thickening of basement membranes**. The thickening is most evident in the capillaries of skeletal muscle, retina, renal glomeruli, and renal medulla. However, it may also be seen in other structures as renal tubules, the Bowman capsule, peripheral nerves, and placenta. By electron microscopy, the basal lamina separating parenchymal or endothelial cells from the blood space is markedly thickened by concentric layers of hyaline material composed predominantly of type IV collagen ([Fig. 20-28](#)). It should be noted that **despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins. The microangiopathy is the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.** Indistinguishable microangiopathy can be found in aged nondiabetic patients, but it is more prominent in individuals with long-standing diabetes.

**Diabetic Nephropathy.** The kidneys are prime targets of diabetes (see also [Chapter 21](#)), second only to myocardial infarction as a cause of death from this disease. Three types of lesions are seen: (1) glomerular lesions; (2) renal vascular lesions, principally arteriolosclerosis; and (3) tubulointerstitial lesions, including necrotizing papillitis.

The most important glomerular lesions are capillary basement membrane thickening, mesangial sclerosis, and nodular glomerulosclerosis. The glomerular capillary basement membrane thickening is present throughout their entire length. This change can be detected by electron microscopy at the onset of diabetes, sometimes without any associated change in renal function ([Fig. 20-28](#)).

**Diffuse mesangial sclerosis** consists of a diffuse increase in mesangial matrix and mesangial cell proliferation and is always associated with basement membrane thickening. It is found in diabetes with disease of more than 10 years' duration. When glomerulosclerosis becomes dominant, it leads to the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema.

**Nodular glomerulosclerosis** describes a glomerular lesion made distinctive by a dense, eosinophilic, laminated matrix situated in the periphery of the glomerulus ([Fig. 20-30](#)). These nodules usually contain trapped mesangial cells. This distinctive change has been called Kimmelstiel-Wilson lesion, after the pathologists who described it. Nodular glomerulosclerosis is encountered in 15% to 30% of long-term diabetics and is a major cause of morbidity and mortality. Diffuse glomerulosclerosis may also be seen in association with old age and hypertension; on the other hand, nodular glomerulosclerosis, once certain unusual forms of nephropathies have been excluded, is essentially pathognomonic of diabetes. Both the diffuse and the nodular forms of glomerulosclerosis are due to sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular surface ([Fig. 20-31](#)).

**Renal atherosclerosis and arteriolosclerosis constitute part of the macrovascular complications in diabetics.** The kidney is one of the most frequently and severely affected organs; the arteries and arterioles are similar to those found throughout the body. **Hyaline arteriosclerosis affects not only the afferent but also the efferent arterioles.** Such efferent arteriolosclerosis is commonly encountered in persons who do not have diabetes.

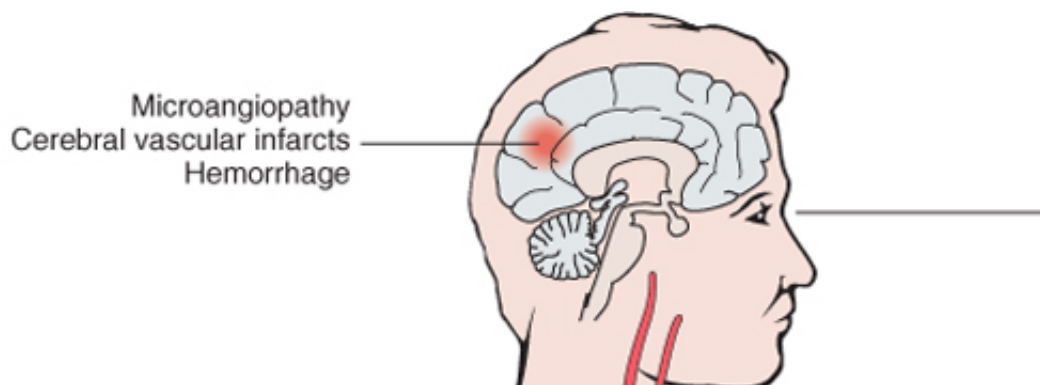
**Pyelonephritis is an acute or chronic inflammation of the kidneys that usually starts in the renal pelvis and then spreads to affect the tubules.** Both the acute and chronic forms occur in nondiabetics as well as in diabetics but are more common in diabetics than in the general population, and once affected, diabetics tend to have more severe involvement. **Chronic pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics.**

**Ocular Complications of Diabetes.** Visual impairment, sometimes even total blindness, are feared consequences of long-standing diabetes. **The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.** Retinopathy, the most common ocular complication, is a constellation of changes that together are considered by many ophthalmologists to constitute the disease. **The lesion in the retina takes two forms: nonproliferative (background) retinopathy and proliferative retinopathy.**

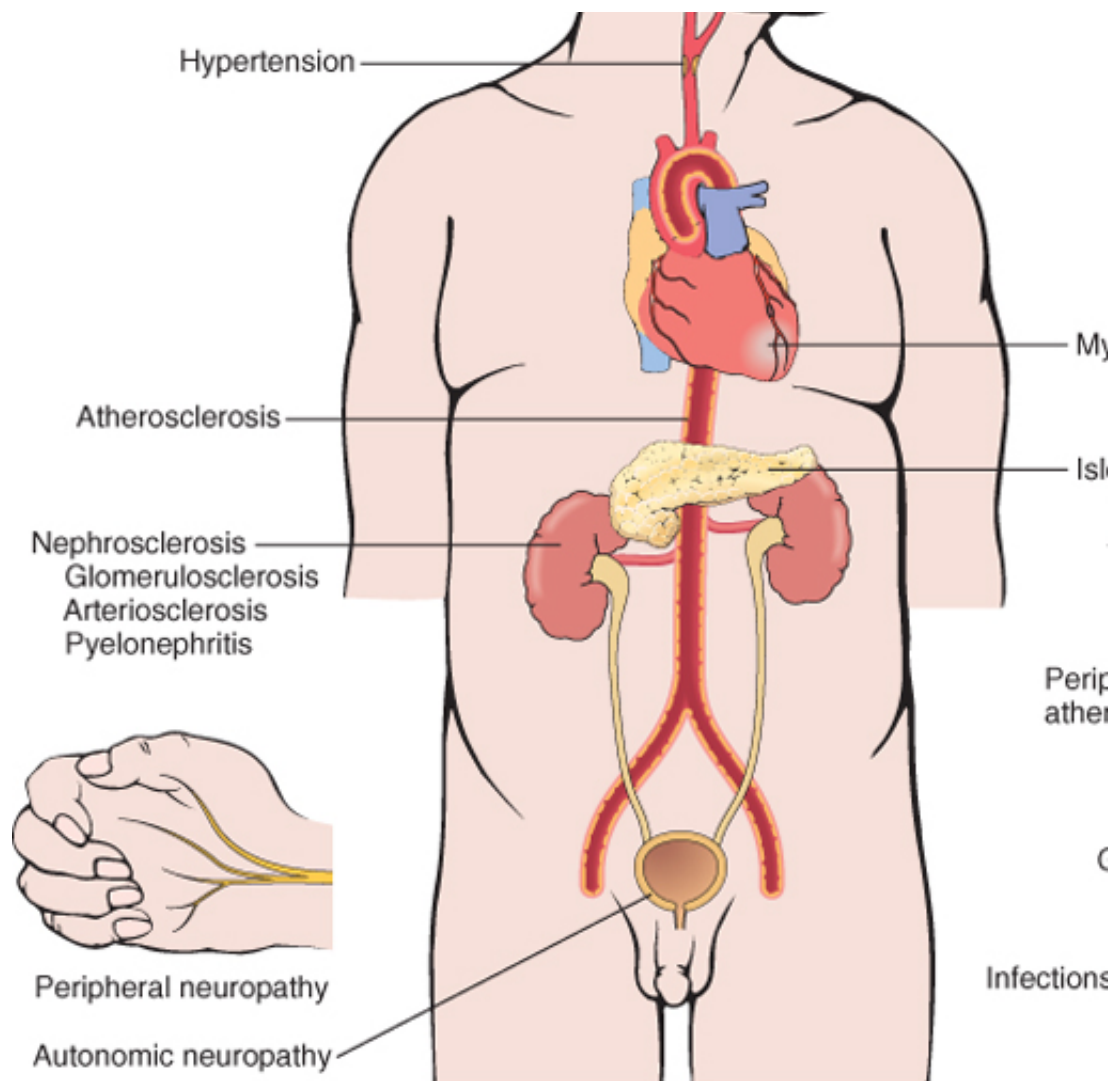
**Nonproliferative retinopathy** includes intraretinal or preretinal hemorrhages, retinal microaneurysms, venous dilations, edema, and, most importantly, thickening of the retina (macular edema). The retinal exudates can be either "soft" (microinfarcts) or "hard" (deposits of cholesterol and lipids) (Fig. 20-32). The microaneurysms are discrete saccular dilations of retinal capillaries that appear through the ophthalmoscope as small red dots. Dilations tend to occur at points of capillary weakening, resulting from loss of pericytes. Retinal edema presumably results from increased capillary permeability. Underlying all of these changes is the microangiopathy, which is thought to be due to capillary pericyte loss and hence to focal weakening of capillary structure.

**The so-called proliferative retinopathy is a process of neovascularization and leads to serious consequences, including blindness, especially if it involves the macula.** The hemorrhages can result from rupture of newly formed capillaries; the resultant organized hemorrhage can pull the retina off its substratum (retinal detachment).

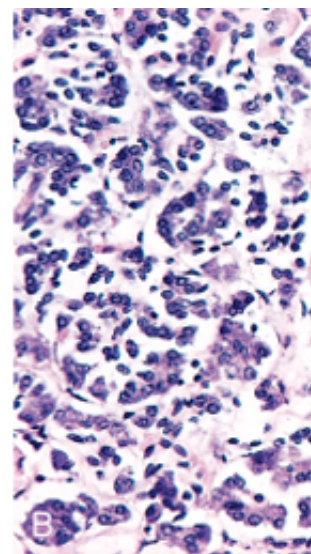
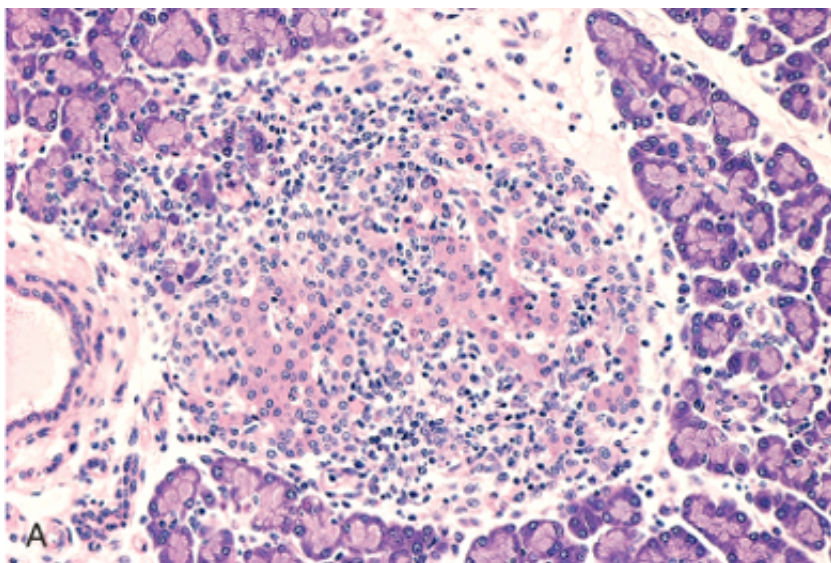
**Diabetic Neuropathy.** The central and peripheral nervous systems are not spared. A frequent pattern of involvement is a peripheral, symmetric neuropathy of the lower extremities, affecting both motor and sensory function but particularly the latter. Other forms include peripheral autonomic neuropathy, which produces disturbances in bowel and bladder function and sometimes sexual impotence. **Mononeuropathy, which may manifest as sudden footdrop, wristdrop, or isolated cranial nerve palsies, neurologic changes may be caused by microangiopathy and increased permeability of the blood vessels supplying the nerves as well as direct axonal damage due to alterations in sorbitol metabolism.**



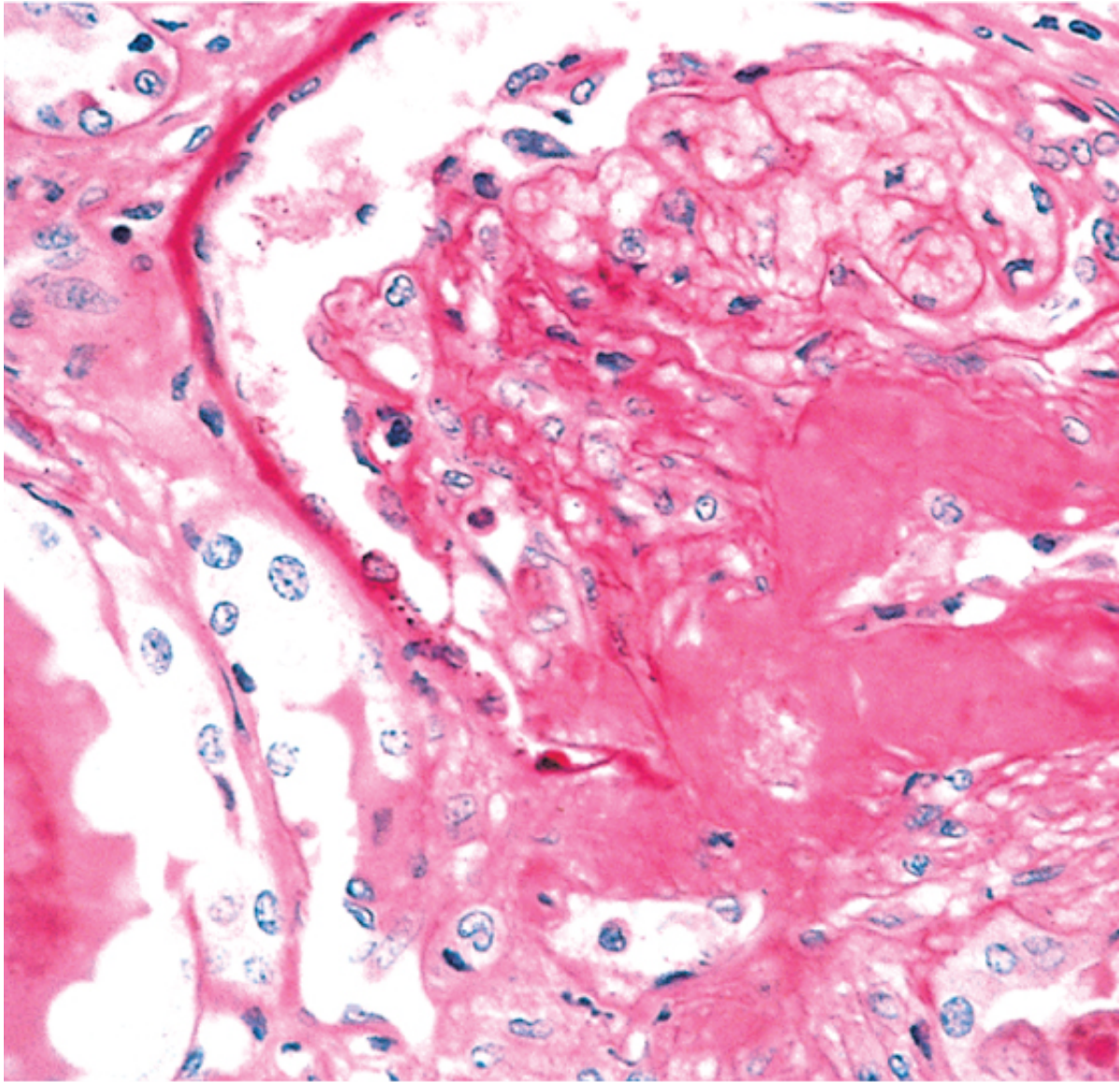




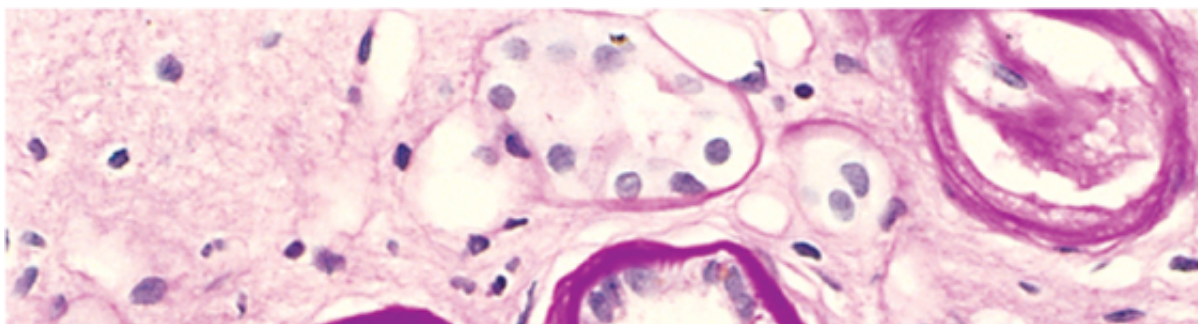
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Figure 20-25 Long-term complications of diabetes.



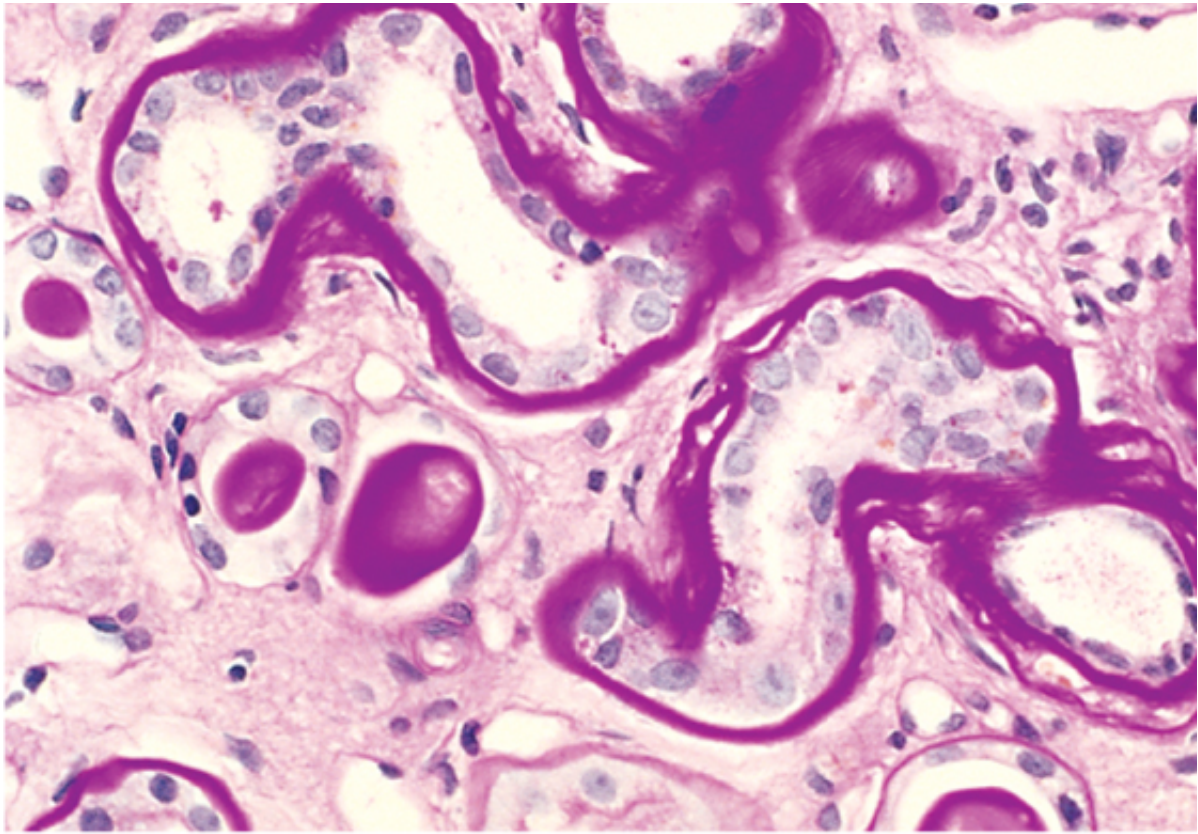
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 Figure 20-26 **A**, Insulitis, shown here from a rat (BB) model of autoimmune diabetes, and seen in type 1 human dia  
 2 diabetes. (**A**, Courtesy of Dr. Arthur Like, University of Massachusetts, Worchester



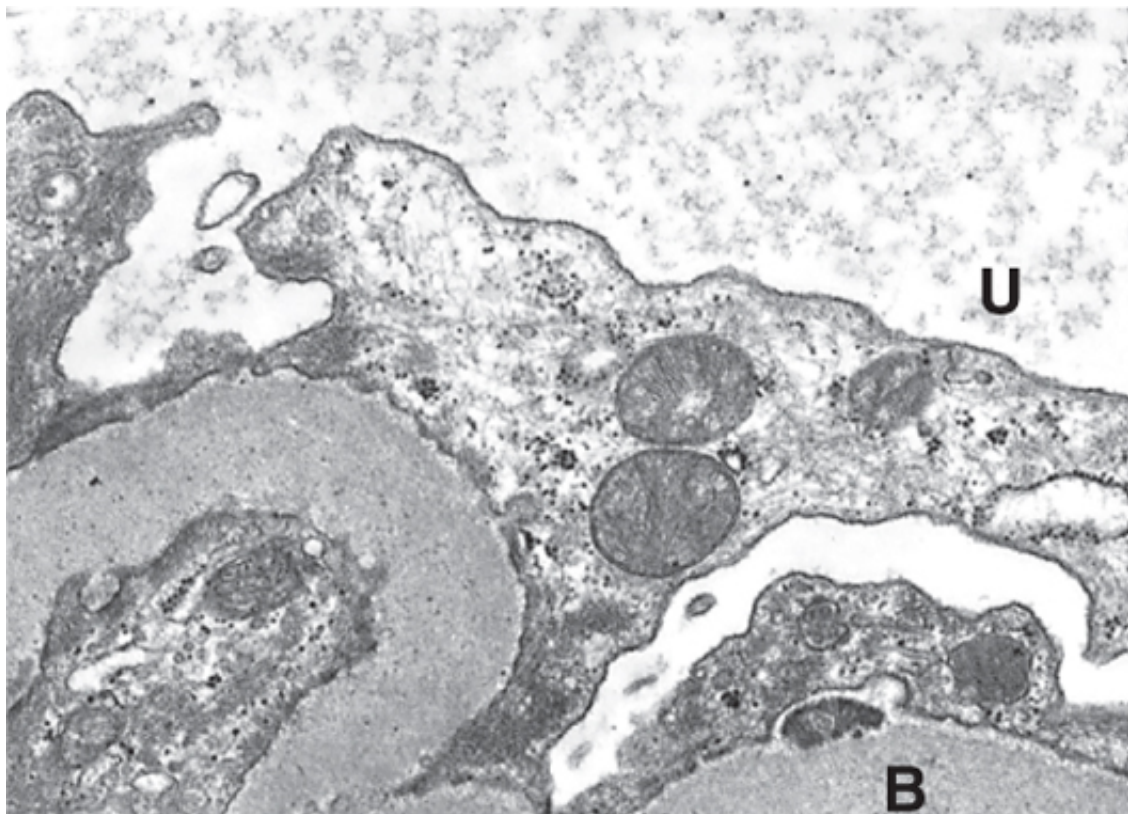
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 Figure 20-27 Severe renal hyaline arteriosclerosis. Note a markedly thickened, tortuous afferent arteriole. The ar  
 evident. (PAS stain; courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas I



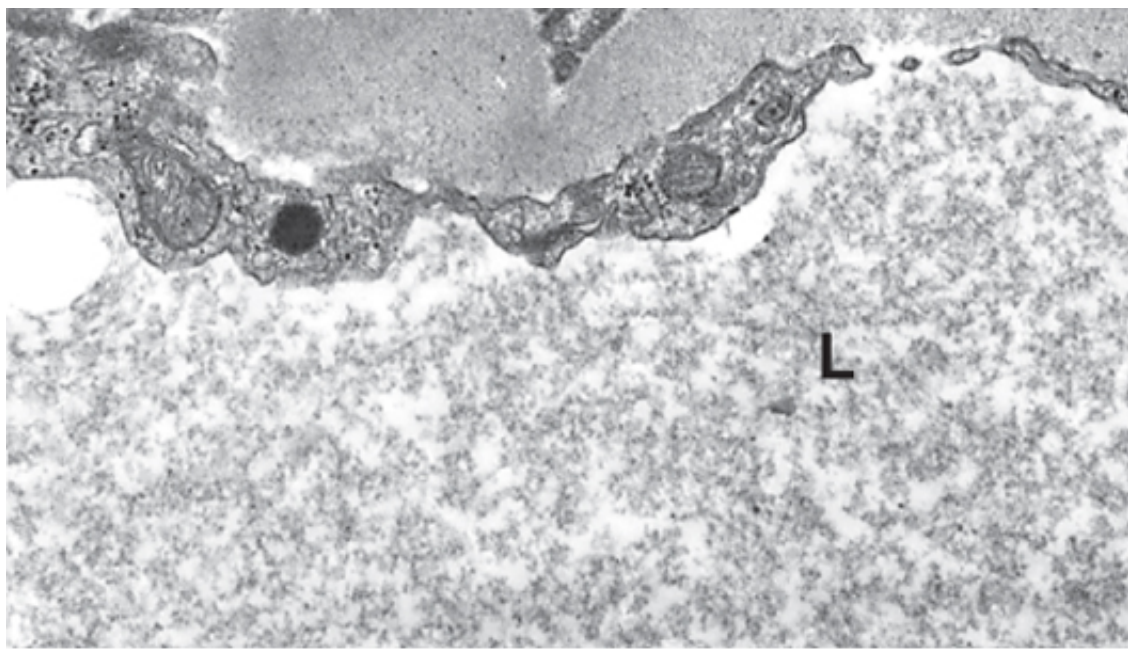




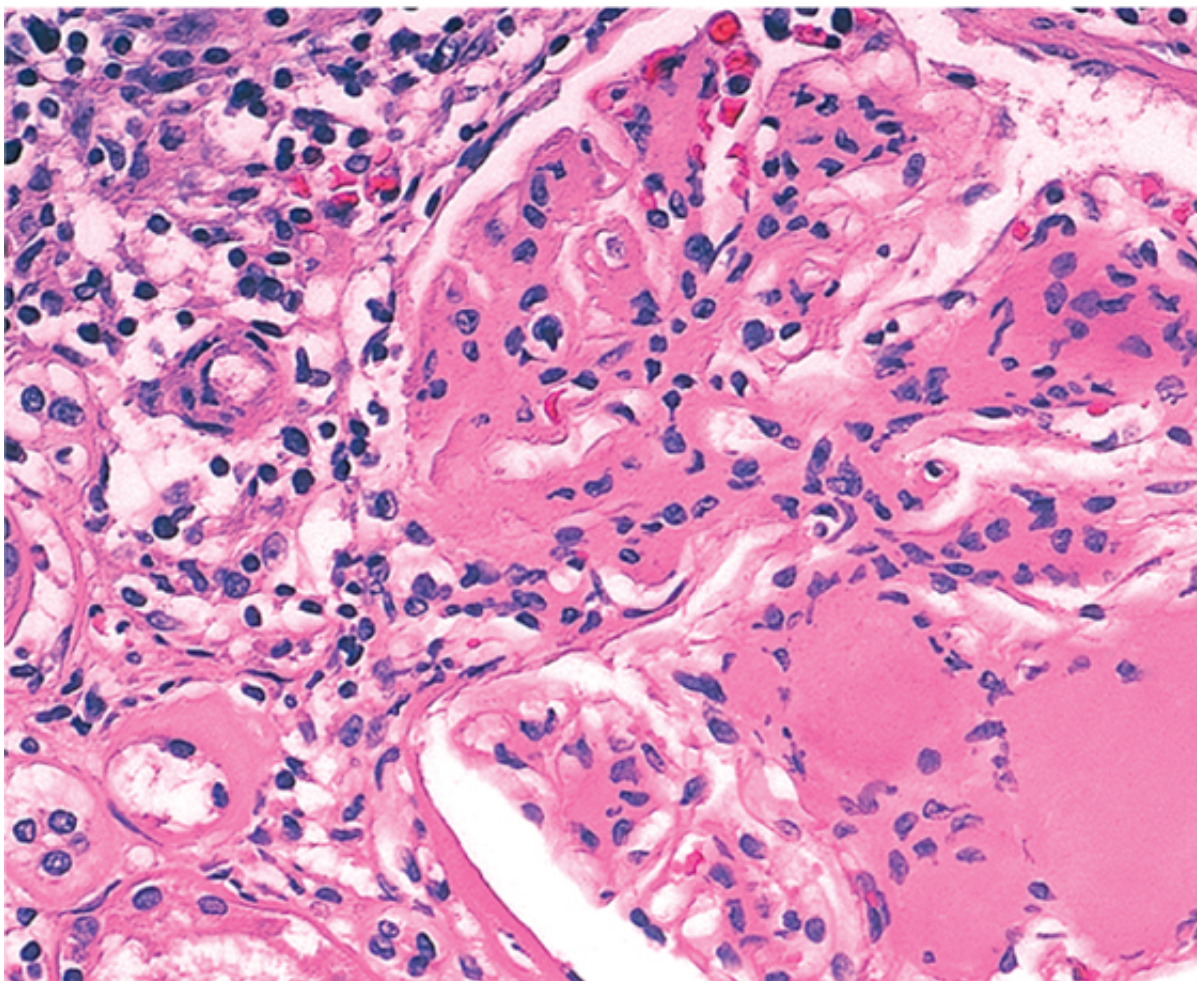
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Figure 20-28 Renal cortex showing thickening of tubular basement membranes in a diabetic patient.



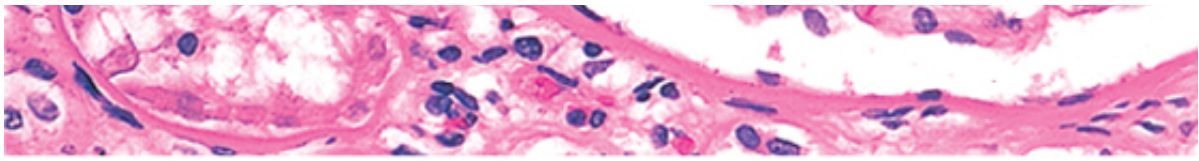




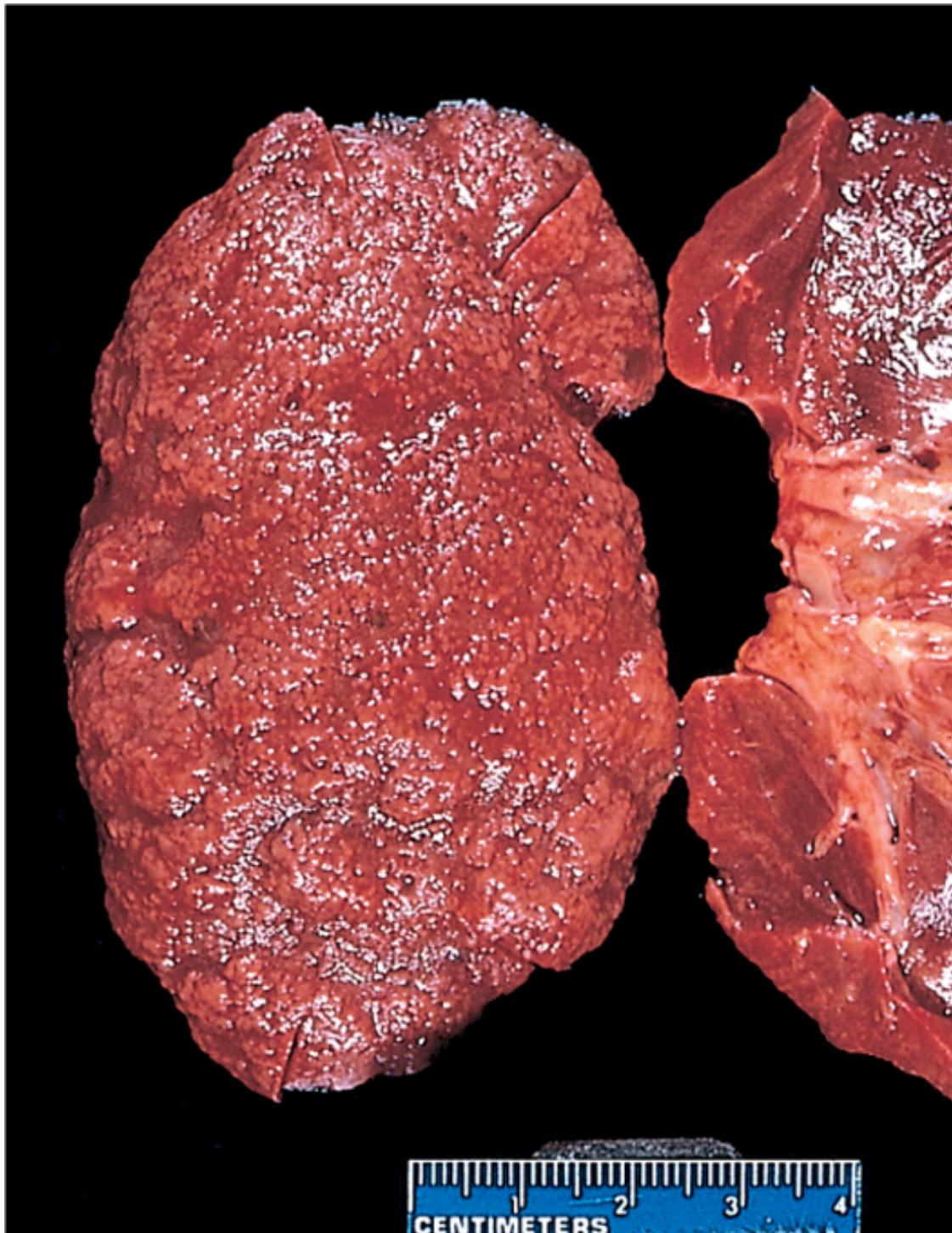
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 Figure 20-29 Renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic. L  
 (Courtesy of Dr. Michael Kashgarian, Department of Pathology, Yale University School of Medicine)





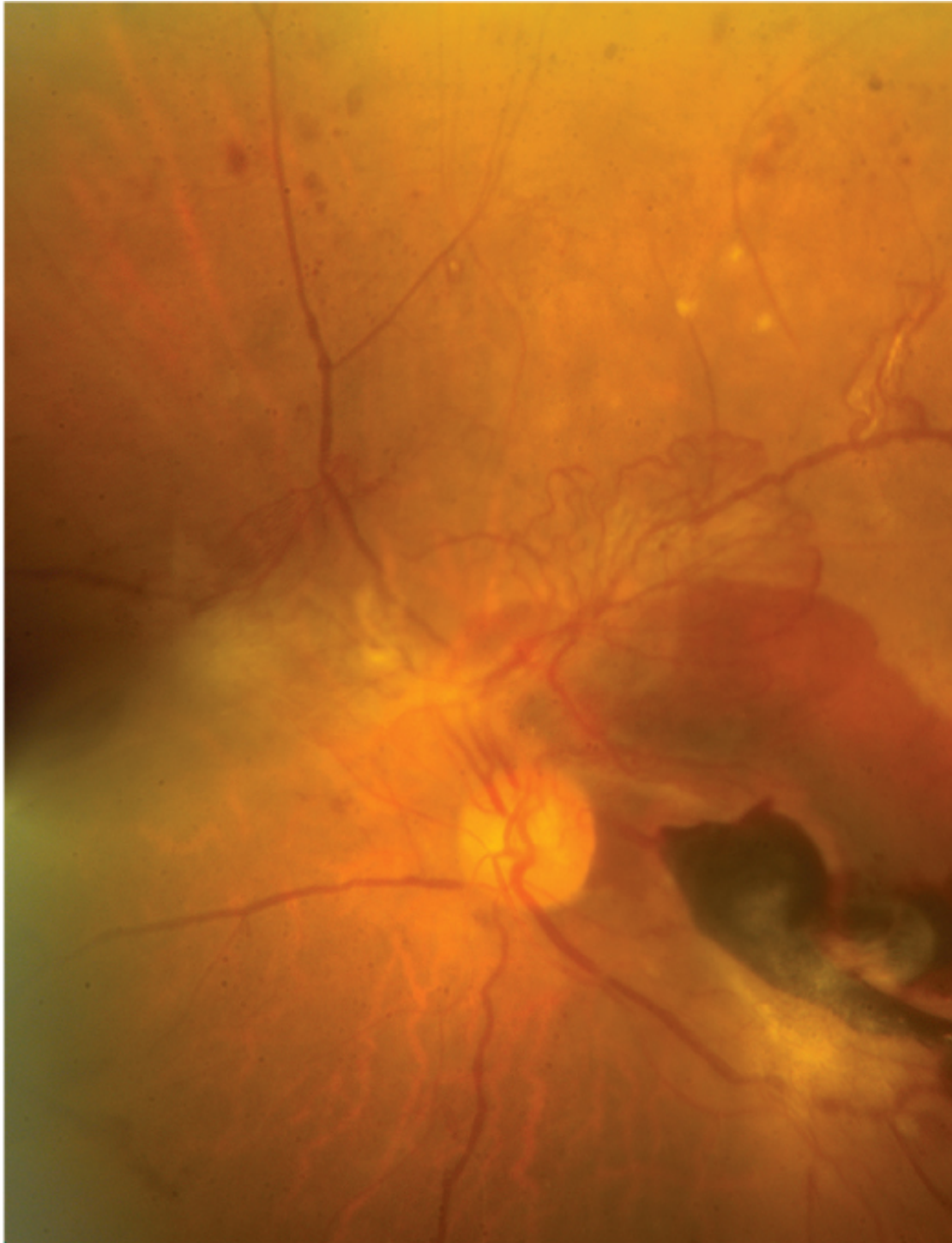


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Figure 20-30 Nodular glomerulosclerosis in a person with long-standing diabetes. (Courtesy of Dr. Lisa Yerian, D  
Chicago, Illinois.)



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Figure 20-31 Nephrosclerosis in a person with long-standing diabetes. The kidney has been bisected to demonstrate the sclerotic surface (*left*) and marked thinning of the cortical tissue (*right*). Additional features include some irregular depressions and a cortical cyst (*far right*).



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Figure 20-32 Diabetic retinopathy, demonstrating advanced proliferative retinopathy with retinal hemorrhages, exudates, and retinal detachment in the lower right corner. (Courtesy of Dr. Rajendra Apte, Washington University School of Medicine)

#### *Clinical Features*

## Clinical Features

It is difficult to sketch with brevity the diverse clinical presentations of diabetes mellitus. Only a few (Table 20-6). In the initial 1 or 2 years following manifestation of overt *type 1 diabetes*, the exogenous insulin requirement is secondary to ongoing endogenous insulin secretion (referred to as the "*honeymoon period*"). The  $\beta$ -cell reserve is exhausted and insulin requirements increase dramatically. Although  $\beta$ -cell destruction from impaired *glucose* tolerance to overt diabetes may be abrupt, heralded by an event with infection. The onset is marked by polyuria, polydipsia, polyphagia, and in severe cases, ketoacidotic derangements (Fig. 20-33). Since insulin is a major anabolic hormone in the body, *deficiency of insulin affects not only glucose metabolism but also fat and protein metabolism*. The assimilation of glucose is sharply diminished or abolished. Not only does storage of glycogen in liver and muscle cease, but glycogenolysis. The resultant hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria causes an osmotic diuresis and thus *polyuria*, causing a profound loss of water and electrolytes. The obligatory hyperosmolarity resulting from the increased levels of *glucose* in the blood tends to deplete intracellular osmoreceptors of the thirst centers of the brain. In this manner, intense thirst (*polydipsia*) appears. The swing from insulin-promoted anabolism to catabolism of proteins and fats. Proteolysis follows, and amino acids are removed by the liver and used as building blocks for *glucose*. The catabolism of proteins and fat stores, which in turn leads to increasing appetite (*polyphagia*), thus completing the classic triad of polyuria, polydipsia, and polyphagia. Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle wasting. Polyphagia and weight loss is paradoxical and should always raise the suspicion of diabetes.

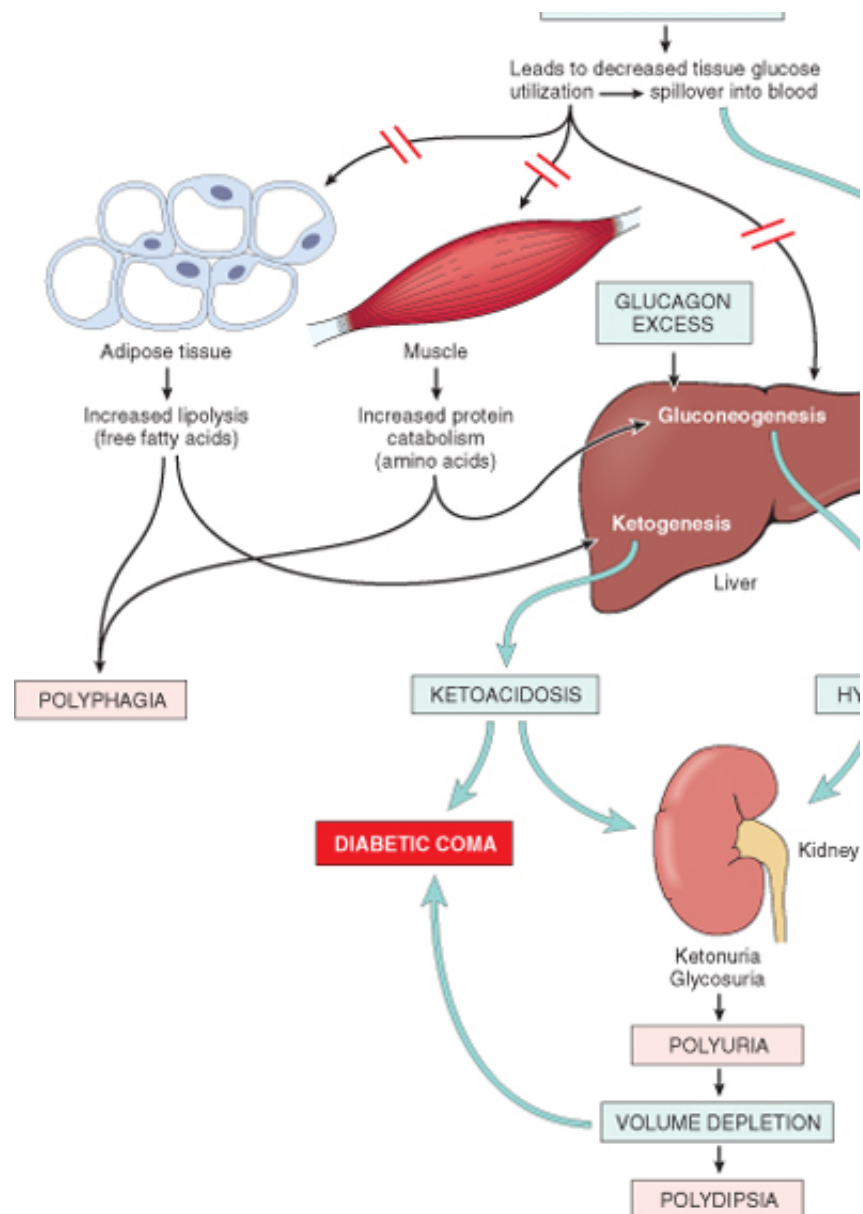
**Table 20-6. Type 1 versus Type 2 Diabetes Mellitus**

Parameter	Type 1	Type 2
<b>Clinical</b>		
	Onset <20 years	Onset >30 years
	Normal weight	Obesity
	Markedly decreased blood insulin	Increased blood insulin (early); decreased (late)
	Antibodies to islet cells	No antibodies to islet cells
	Ketoacidosis common	Ketoacidosis rare; nonketotic hyperosmolar coma
<b>Genetics</b>		
	30% to 70% concordance in twins	50% to 90% concordance
	Linkage to MHC class II HLA genes	No HLA linkage Linkage to candidate "diabetes" genes
<b>Pathogenesis</b>		
	Autoimmune destruction of $\beta$ -cells mediated by T cells and humoral mediators	Insulin resistance in skeletal muscle and liver
	Absolute insulin deficiency	$\beta$ -cell dysfunction and relative insulin deficiency
<b>Islet cells</b>		
	Insulinitis early	No insulinitis
	Marked atrophy and fibrosis	Focal atrophy and amyloidosis
	$\beta$ -cell depletion	Mild $\beta$ -cell depletion

HLA, human leukocyte antigen; MHC, major histocompatibility complex.







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Figure 20-33 Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus. An absolute insulin deficiency leads to hyperglycemia, which causes osmotic diuresis and dehydration. This is compounded by excessive breakdown of adipose stores, giving rise to increased levels of FFAs, oxidation of which generates ketones. Ketogenesis is an adaptive phenomenon in times of starvation, generating ketones as a source of energy (e.g., brain). The rate at which ketone bodies are formed may exceed the rate at which they can be excreted, leading to ketonemia and ketonuria. If the urinary excretion of ketones is compromised by dehydration, the pH decreases, resulting in metabolic ketoacidosis.

In individuals with type 1 diabetes, deviations from normal dietary intake, unusual physical activity may rapidly influence the treacherously fragile metabolic balance, predisposing one to *diabetic ketoacidosis* usually in the range of 500 to 700 mg/dL as a result of absolute insulin deficiency and unopposed (epinephrine<sup>®</sup>, glucagon). The marked hyperglycemia causes an osmotic diuresis and dehydration. The second major effect is activation of the ketogenic machinery. Insulin deficiency leads to activation of the ketogenic machinery, giving rise to excessive breakdown of adipose stores, giving rise to increased levels of FFAs, oxidation of which generates ketones. Ketogenesis is an adaptive phenomenon in times of starvation, generating ketones as a source of energy (e.g., brain). The rate at which ketone bodies are formed may exceed the rate at which they can be excreted, leading to ketonemia and ketonuria. If the urinary excretion of ketones is compromised by dehydration, the pH decreases, resulting in metabolic ketoacidosis.



*Type 2 diabetes mellitus* may also present with polyuria and polydipsia, but unlike type 1 diabetes frequently obese. However, with the increase in obesity and sedentary life style in our society, type 2 diabetes is becoming increasingly frequent. In some cases medical attention is sought because of symptoms, frequently, however, the diagnosis is made after routine blood or urine testing in asymptomatic patients.

In the decompensated state, individuals with type 2 diabetes may develop *hyperosmolar nonketotic* severe dehydration resulting from sustained osmotic diuresis in patients who do not drink enough from chronic hyperglycemia. Typically, the person is an elderly diabetic who is disabled by a stroke or inadequate water intake. Furthermore, the absence of ketoacidosis and its symptoms (nausea, vomiting) may lead to seeking of medical attention in these patients until severe dehydration and coma occur.

As previously discussed, it is the long-term effects of diabetes, more than the acute metabolic complications, that constitute the overwhelming proportion of morbidity and mortality attributable to this disease. In most instances, approximately 15 to 20 years after the onset of hyperglycemia.

*In both forms of long-standing diabetes, cardiovascular events such as myocardial infarction and cerebrovascular accidents are the most common causes of mortality.* The impact of cardiovascular involvement is as high as 80% of deaths of type 2 diabetics; in fact, diabetics have a 3 to 4 times higher risk of death from cardiovascular causes than nondiabetic populations. The hallmark of cardiovascular disease in diabetes is large and medium-sized arteries (i.e., macrovascular disease). The importance of *obesity* has already been discussed, but it is also an independent risk factor for development of atherosclerosis, a leading cause of end-stage renal disease in the United States. The earliest manifestation of diabetic nephropathy is the presence of small amounts of albumin in the urine (>30 mg/day, but <300 mg/day; i.e., *microalbuminuria*). Approximately 80% of type 1 diabetics and 20% to 40% of type 2 diabetics will develop overt nephropathy (>300 mg/day) over the next 10 to 15 years, usually accompanied by the appearance of hypertension. The progression from *microalbuminuria* to *end-stage renal disease* can be highly variable and is evidenced by a progressive increase in serum creatinine. By 20 years after diagnosis, more than 75% of type 1 diabetics and about 20% of type 2 diabetics develop end-stage renal disease, requiring dialysis or renal transplantation. *Visual impairment* is one of the more feared consequences of long-standing diabetes. This disease is currently the leading cause of blindness in the United States. Approximately 60% to 80% of patients develop some form of retinopathy within 10 to 20 years after diagnosis. In addition to retinopathy, diabetics also have an increased prevalence of cataracts and glaucoma. *Diabetic neuropathy* typically involves the distal extremities with less evident motor abnormalities (sensorimotor neuropathy). The development of ulcers that heal poorly and are a major cause of morbidity. As many as 20% of diabetics develop autonomic dysfunction over time, as manifested by impediments in bowel and bladder control. *Enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and other infections*, are also common. In an individual with diabetic neuropathy, a trivial infection can lead to a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death.



## PANCREATIC ENDOCRINE NEOPLASMS

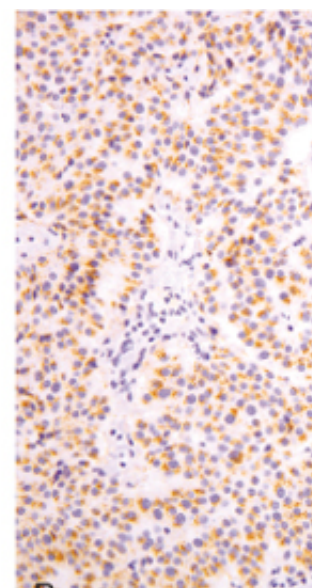
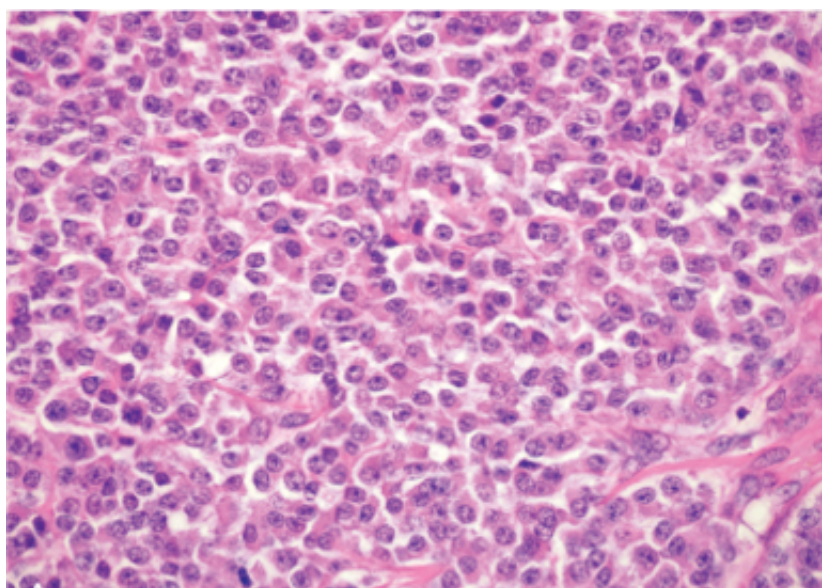
*Pancreatic endocrine neoplasms*, also known as "islet cell tumors," are rare in comparison with tumors of the exocrine pancreas, accounting for only 2% of all pancreatic neoplasms. They are most common in adults, may be benign or malignant, and may metastasize to lymph nodes and liver. Pancreatic endocrine neoplasms have a propensity for functional activity, but some may be totally nonfunctional. Like any other endocrine neoplasms, it is difficult to predict the behavior of a pancreatic endocrine neoplasm purely on the basis of light microscopic criteria. In general, tumors less than 2 cm in diameter are benign, but there are significant exceptions to this rule. The functional status of the tumor may have prognostic significance. Approximately 90% of insulinomas are benign, while 60% to 90% of other functioning and nonfunctioning endocrine neoplasms tend to be malignant. Fortunately, insulinomas are also the most common subtype of pancreatic endocrine neoplasms.

### Insulinomas

$\beta$ -cell tumors (insulinomas) are the most common of pancreatic endocrine neoplasms and may be benign or malignant. They secrete sufficient insulin to induce clinically significant hypoglycemia. There is a characteristic clinical triad: (1) attacks of hypoglycemia occur with blood glucose amounts below 50 mg/dL of serum; (2) the nervous system manifestations as confusion, stupor, and loss of consciousness; and (3) the attacks are promptly relieved by feeding or parenteral administration of glucose.

#### Morphology

Insulinomas are most often found within the pancreas and are generally benign. Multiple tumors or tumors ectopic to the pancreas may be encountered. Making up only about 10% of cases, they are diagnosed on the basis of criteria for malignancy. Solitary tumors are usually small (often <2 cm in diameter) and are encapsulated, well-circumscribed, and located anywhere in the pancreas. Histologically, these benign tumors look remarkably like normal islets of Langerhans, with preservation of the regular cords of monotonous cells and their orientation to the vascular spaces. Malignant lesions present much evidence of anaplasia (Fig. 20-34A), and they may be poorly circumscribed or nonencapsulated. By immunocytochemistry, insulin can be localized in the tumor cells. At the electron microscope, neoplastic  $\beta$  cells, like their normal counterparts, display distinct dense granules. However, one should be cautioned that granules may be present in the absence of clinically significant insulin production.





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Figure 20-34 Pancreatic endocrine tumor ("islet cell tumor"). **A**, The neoplastic cells are monotonous and demonstrate uniform nuclei (H&E stain). **B**, Immunoreactivity for insulin confirms the neoplasm is an insulinoma. Clinically, the patient had hypoglycemia.

While as many as 80% of islet cell tumors may demonstrate excessive insulin secretion, hypoglycemia cases never become clinically symptomatic. The critical laboratory findings in insulinomas are high insulin-to-glucose ratio. Surgical removal of the tumor is usually followed by prompt reversal of the hypoglycemia. *there are many other causes of hypoglycemia besides insulinomas.* These include diffuse liver disease, growth factor-2 (IGF-2) by some fibrosarcomas, and self-injection of insulin.

### Gastrinomas

Marked hypersecretion of gastrin usually has its origin in gastrin-producing tumors (*gastrinomas*), duodenum and peripancreatic soft tissues as in the pancreas (so-called "gastrinoma triangle"). Zollinger-Ellison syndrome is the association of pancreatic islet cell lesions with hypersecretion of gastric acid and severe peptic ulcer disease in 95% of patients (Zollinger-Ellison syndrome).

#### Morphology

Gastrinomas may arise in the pancreas, the peripancreatic region, or the wall of the duodenum. **gastrin-producing tumors are locally invasive or have already metastasized at the time of diagnosis.** In approximately 25% of patients, gastrinomas arise in conjunction with other endocrine tumors conforming to the MEN-1 syndrome (see below); MEN-1-associated gastrinomas are usually multiple, while sporadic gastrinomas are usually single. As with insulin-secreting tumors of the pancreas, gastrin-producing tumors are histologically bland and rarely exhibit marked anaplasia.

In Zollinger-Ellison syndrome, hypergastrinemia from a pancreatic or duodenal tumor stimulates excessive gastric acid secretion, which in turn causes *peptic ulceration*. The duodenal and gastric ulcers are often *multiple*; although they are common in this population, they are often *intractable* to usual modalities of therapy. In addition, ulcers may also occur in the jejunum; when intractable jejunal ulcers are found, Zollinger-Ellison syndrome should be considered. Diarrhea; in 30% it is the presenting symptom.

### Other Rare Pancreatic Endocrine Neoplasms

$\alpha$ -Cell tumors (*glucagonomas*) are associated with increased serum glucagon and a syndrome characterized by a characteristic skin rash (*necrolytic migratory erythema*), and anemia. They occur most frequently in women and are characterized by extremely high plasma glucagon levels.  $\delta$ -Cell tumors (*somatostatinomas*) cause diabetes mellitus, cholelithiasis, steatorrhea, and hypochlorhydria. They are exceedingly difficult to diagnose; high plasma somatostatin levels are required for diagnosis. *VIPoma* (*watery diarrhea, hypokalemia, and achlorhydria*) is an endocrine tumor that induces the eponymous characteristic syndrome, caused by release of vasoactive intestinal peptide from the tumor. Some of these tumors are locally invasive and metastatic.





## ADRENAL CORTEX

The *adrenal glands* are paired endocrine organs consisting of both cortex and medulla, which differ in their development, structure, and function. The *cortex* consists of three layers of distinct cell types. Beneath the capsule of the adrenal is the narrow layer of zona glomerulosa. An equally narrow zona reticularis abuts the medulla. Intervening is the broad zona fasciculata, which makes up about 75% of the total cortex. The adrenal cortex synthesizes three different types of steroids: (1) *glucocorticoids* (principally cortisol), which are synthesized primarily in the zona fasciculata with a small contribution from the zona reticularis; (2) *mineralocorticoids*, the most important being aldosterone, which is generated in the zona glomerulosa; and (3) *sex steroids* (estrogens and androgens), which are produced largely in the zona reticularis. The *adrenal medulla* is composed of chromaffin cells, which synthesize and secrete *catecholamines*, mainly *epinephrine*<sup>®</sup>. This section deals first with disorders of the adrenal cortex and then of the medulla. Diseases of the adrenal cortex can be conveniently divided into those associated with cortical hyperfunction and those characterized by cortical hypofunction.







## ADRENOCORTICAL HYPERFUNCTION (HYPERADRENALISM)

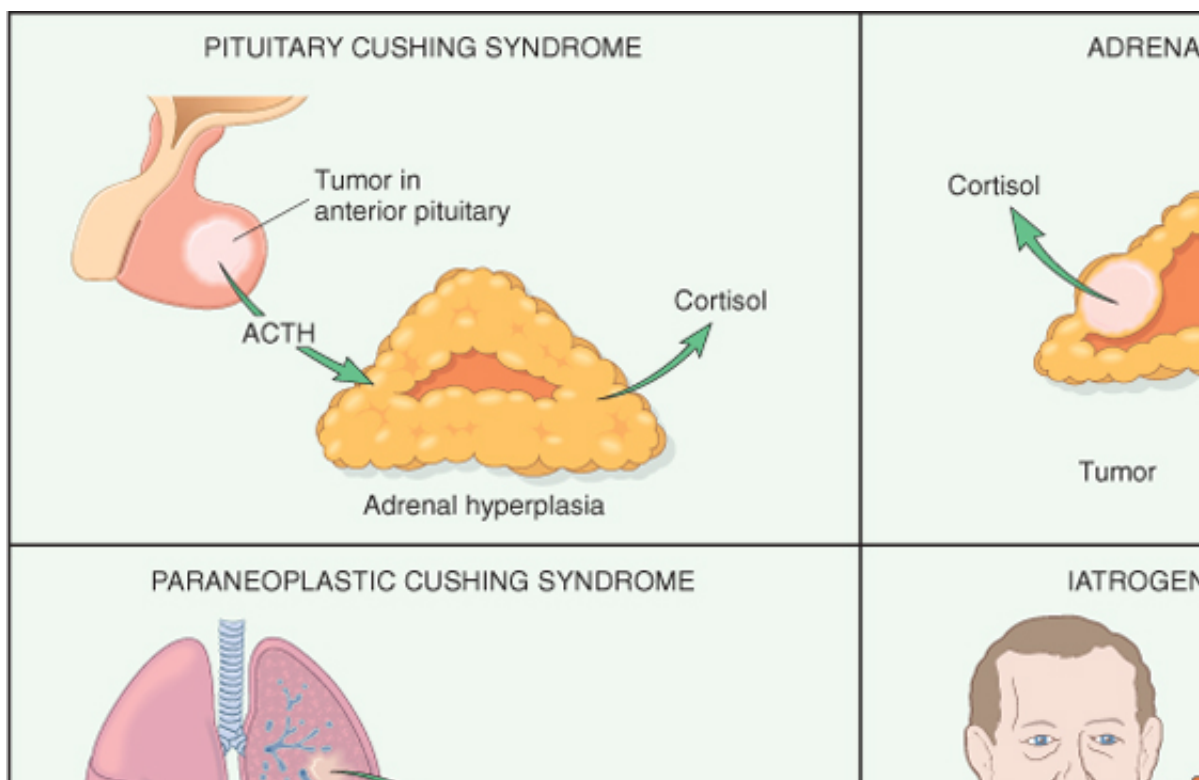
Just as there are three basic types of corticosteroids elaborated by the adrenal cortex (glucocorticosteroids), so there are three distinctive hyperadrenal clinical syndromes: (1) *Cushing syndrome*, caused by an excess of glucocorticoids; (2) *hyperaldosteronism*; and (3) *adrenogenital* or virilizing syndromes, caused by an excess of androgens. These syndromes overlap somewhat because of the overlapping functions of some of the adrenal

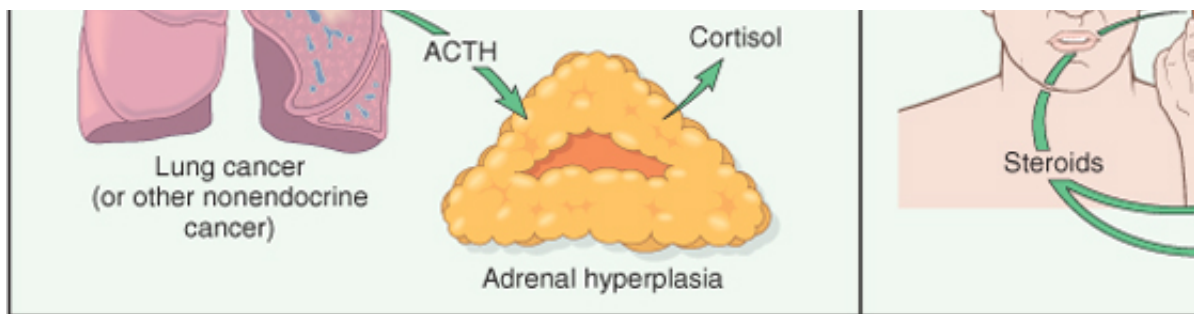
### Hypercortisolism (Cushing Syndrome)

This disorder is caused by any condition that produces an elevation in glucocorticoid levels. *In clinical practice, most cases of Cushing syndrome are caused by the administration of exogenous glucocorticoids.* The remaining cases are caused by the following (Fig. 20-35):

Primary hypothalamic-pituitary diseases associated with hypersecretion of ACTH  
 Primary adrenal neoplasia  
 The secretion of ectopic ACTH by nonendocrine neoplasms

Primary hypothalamic-pituitary disease associated with oversecretion of ACTH, also known as *Cushing disease*, accounts for about half of the cases of spontaneous, endogenous Cushing syndrome. The disorder affects women and men, and it occurs most frequently during the 20s and 30s. In the vast majority of cases, the *pituitary gland* contains a *microadenoma* that does not produce mass effects in the brain; some corticotroph tumors qualify as *adenomas*. In the remaining patients, the anterior pituitary contains areas of *corticotroph cell hyperplasia* without a discrete tumor. *Hyperplasia* may be primary, or arise secondarily from excessive stimulation of ACTH release by a hypothalamic *growth hormone-releasing hormone*-producing tumor. The adrenal glands in patients with Cushing disease are characterized by *cortical hyperplasia* (discussed later), caused by elevated levels of ACTH. The cortical hyperplasia is a form of *hypercortisolism*.





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Figure 20-35 Schematic representation of the various forms of Cushing syndrome, illustrating the three endogenous (iatrogenic) form. ACTH, adrenocorticotrophic hormone.

*Primary adrenal neoplasms*, such as adrenal adenoma and carcinoma, and *primary cortical hyperplasia* account for about 20% of cases of endogenous Cushing syndrome. This form of Cushing syndrome is also designated *adrenal Cushing syndrome* because the adrenals function autonomously. The biochemical hallmark is elevated levels of cortisol with low serum levels of ACTH. In most cases, adrenal Cushing syndrome is caused by an *adrenocortical neoplasm*, which may be either benign (adenoma) or malignant (carcinoma). *Primary pigmented nodular adrenocortical disease* is a rare cause of Cushing syndrome. There are two variants of this entity; the first presents as large nodules, and the second as micronodules (>3 mm) that are often pigmented ("primary pigmented nodular adrenocortical disease"). The latter is a familial disease, usually associated with features of overactivity in other endocrine organs such as the parathyroids.

*Secretion of ectopic ACTH by nonendocrine tumors* accounts for most of the remaining cases of endogenous Cushing syndrome. Commonly, the responsible tumor is a *small-cell carcinoma of the lung*, although other neoplasms such as *carcinomas of the thyroid*, and *islet cell tumors of the pancreas*, have also been associated with this syndrome. In addition to elaborate ectopic ACTH, an occasional neoplasm produces ectopic corticotropin-releasing hormone, which also causes hypercortisolism. As with Cushing syndrome associated with hypothalamic-pituitary disease, the hypercortisolism is due to excessive stimulation of the adrenals.

### Morphology

The main lesions of Cushing syndrome are found in the pituitary and adrenal glands. The morphological changes in the pituitary in Cushing syndrome show changes regardless of the cause. The most common alteration is the presence of **Crooke hyaline change** in the anterior pituitary. This is characterized by the replacement of the normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary by a homogeneous, lightly basophilic material. This alteration is the result of the accumulation of keratin filaments in the cytoplasm.

The morphology of the **adrenal glands** depends on the cause of the hypercortisolism. In the majority of cases, one of the following abnormalities is present: (1) cortical atrophy; (2) diffuse hyperplasia; (3) nodular hyperplasia; or (4) an adenoma, rarely a carcinoma. In patients in whom the syndrome results from exogenous administration of glucocorticoids, suppression of endogenous ACTH results in bilateral **cortical atrophy**. In the absence of exogenous stimulation of the zonae fasciculata and reticularis by ACTH. The zona glomerulosa, which functions independently of ACTH. In the absence of hypercortisolism, in contrast, the adrenals either are hyperplastic or contain a cortical neoplasm. **Diffuse hyperplasia** is found in 60% to 70% of cases of endogenous Cushing syndrome. The adrenal cortex is diffusely thickened and yellow, as a result of an increase in the size and number of cells in the zonae fasciculata and reticularis. Some degree of nodularity is common but is not diagnostic. **Nodular hyperplasia** (Fig. 20-36). This takes the form of bilateral, 0.5- to 2.0-cm, yellow nodules that are separated from the cortex by intervening areas of widened cortex. The combined adrenal weight is usually increased to 30 to 50 gm. This macronodularity appears to be an extension of the diffuse hyperplasia. The nodules between the nodules exactly resembles that found in the diffuse form of this condition. **Adrenocortical neoplasms** causing Cushing syndrome may be malignant or benign. **Adenomas** are yellow tumors surrounded by thin or well-developed capsules, and

gm (Fig. 20-37). Their morphology is identical to that of nonfunctional adenomas associated with hyperaldosteronism (see below). Microscopically, they are composed of cells similar to those encountered in the normal zona fasciculata. The **carcinomas** associated with hyperaldosteronism, by contrast, tend to be larger than the adenomas. These tumors are unencapsulated and may exceed 200 to 300 gm in weight, having all of the anaplastic characteristics of carcinoma. With both functioning benign and malignant tumors, the adjacent adrenal cortex and the rest of the adrenal gland are atrophic because of suppression of endogenous ACTH by high circulating levels of aldosterone.



Figure 20-36 Adrenocortical hyperplasia. The adrenal cortex (bottom) is yellow, thickened, and multinodular as a result of hyperplasia of the cells of the rich zonae fasciculata and reticularis. The top shows a normal adrenal for comparison.

### Clinical Features



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 Figure 20-37 Adrenocortical adenoma. The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. However, an adrenocortical adenoma cannot be predicted from its gross or microscopic appearance.

The signs and symptoms of Cushing syndrome are an exaggeration of the known actions of glucocorticoids.



The signs and symptoms of Cushing syndrome are an exaggeration of the known actions of glucocorticoids. Cushing syndrome develops gradually and, like many other endocrine abnormalities, may be quite subtle in its early stages. The onset is Cushing syndrome associated with small-cell carcinomas of the lung, where the rapid course of development of many of the characteristic features. Early manifestations of Cushing syndrome include weight gain. Over time, the more characteristic centripetal distribution of adipose tissue becomes apparent, with resultant accumulation of fat in the posterior neck and back ("buffalo hump"). Hypercortisolism causes selective atrophy of myofibers, with resultant decreased muscle mass and proximal limb weakness. Glucocorticoids inhibit the uptake of **glucose** by cells, with resultant *hyperglycemia*, *glucosuria*, and *polydipsia*, mimicking the effects of diabetes. Glucocorticoids cause loss of collagen and resorption of bone. Thus, the skin is thin, fragile, and easily bruised, common in the abdominal area. Bone resorption results in the development of *osteoporosis*, with resultant fractures. Because glucocorticoids suppress the immune response, patients with Cushing syndrome are prone to infections. Additional manifestations include *hirsutism* and *menstrual abnormalities*, as well as psychiatric changes including mood swings, depression, and frank psychosis. Extra-adrenal Cushing syndrome caused by a pituitary microadenoma is usually associated with increased skin pigmentation, because of melanocyte-stimulating activity.

## SUMMARY

**Hypercortisolism (Cushing syndrome)** The most common cause of hypercortisolism is the administration of steroids. Endogenous hypercortisolism is most often secondary to a pituitary microadenoma ("Cushing disease"), followed by primary ("ACTH-independent" hypercortisolism), and paraneoplastic ACTH production (e.g., small-cell lung cancer). The morphologic features in the adrenal include bilateral cortical hyperplasia (in exogenous steroid-induced disease), bilateral diffuse or nodular hyperplasia (in endogenous Cushing syndrome), or an adrenocortical neoplasm.

## Hyperaldosteronism

Excessive levels of aldosterone cause *sodium retention and potassium excretion, with resultant hypertension*. Hyperaldosteronism may be primary, or it may be secondary to an extra-adrenal cause. In secondary hyperaldosteronism, aldosterone release occurs in response to activation of the renin-angiotensin system. It is characterized by findings commonly encountered in conditions associated with:

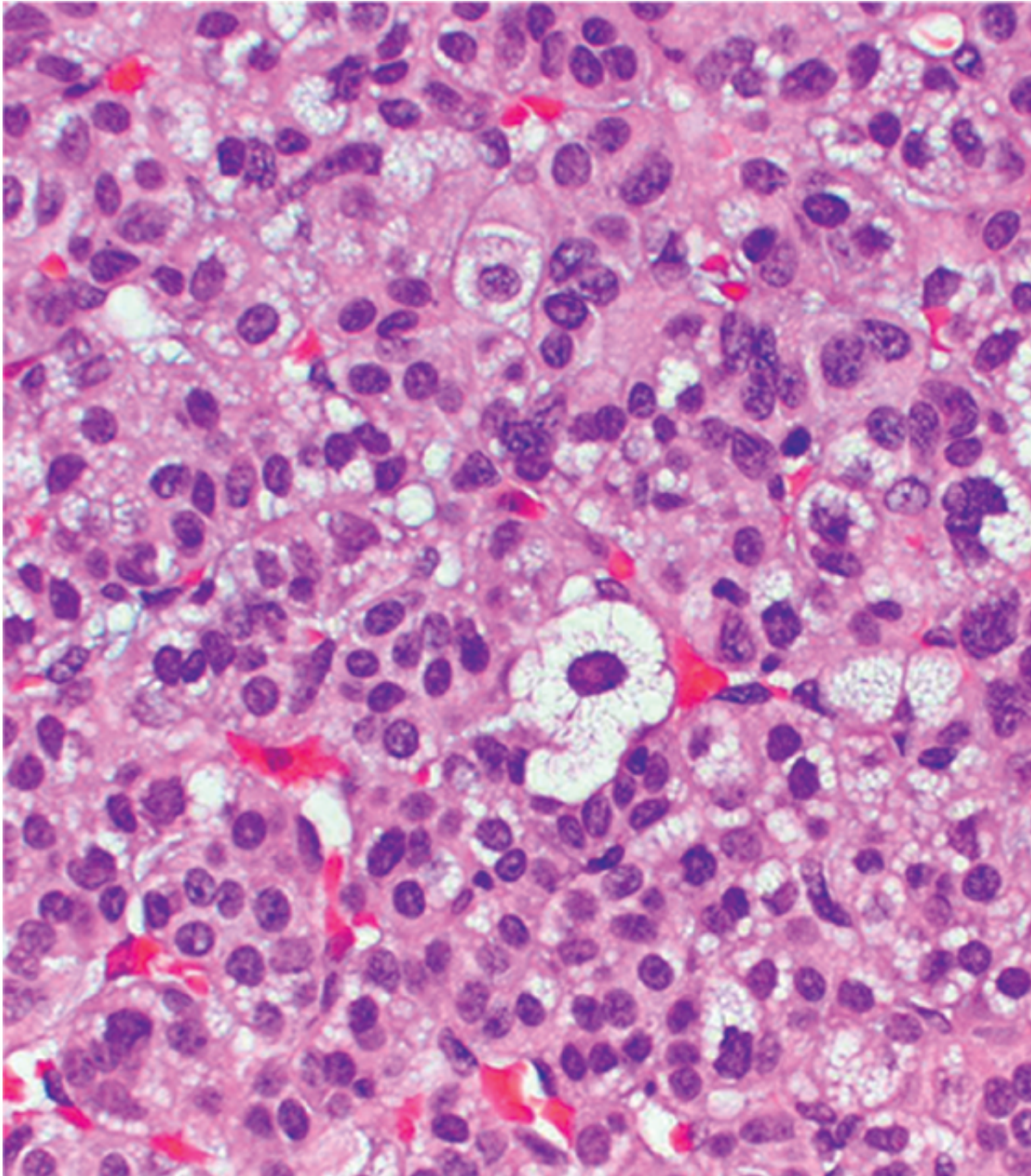
Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis) Arterial hypovolemia (heart failure, cirrhosis, nephrotic syndrome) Pregnancy (caused by estrogen-induced increases in renin)

*Primary hyperaldosteronism*, in contrast, indicates a primary, autonomous overproduction of aldosterone by the adrenal gland, independent of the renin-angiotensin system and *decreased plasma renin activity*. Primary hyperaldosteronism is caused by an adrenocortical neoplasm, usually an adenoma, or by primary adrenocortical hyperplasia. Some cases are caused by overactivity of the aldosterone synthase gene, *CYP11B2*.

## Morphology

In roughly 80% of cases, primary hyperaldosteronism is caused by an **aldosterone-producing adenoma** of one adrenal gland, a condition referred to as **Conn syndrome**. In most cases, the adenoma is small (<2 cm in diameter), encapsulated lesions, although multiple adenomas may occur in an occasional patient; carcinomas resulting in hyperaldosteronism are rare. In contrast to the hypercortisolism associated with Cushing syndrome, those associated with hyperaldosteronism do not involve ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral adrenal are normal. They are bright yellow on cut section and, surprisingly, are composed of lipid-laden cells resembling fasciculata cells rather than glomerulosa cells (the normal source of aldosterone). They tend to be uniform in size and shape; occasionally there is some nuclear atypia and mitotic activity (Fig. 38). A characteristic feature of aldosterone-producing adenomas is the presence of cytoplasmic inclusions, known as **spironolactone bodies**. These are typically formed by the anti-hypertensive drug **spironolactone**, which is the drug of choice in primary hyperaldosteronism. In about 15% of cases, primary hyperaldosteronism is caused by bilateral **primary aldosteronism**, characterized by bilateral nodular hyperplasia of the adrenal glands.

**hyperplasia**, characterized by bilateral nodular hyperplasia of the adrenal glands, found in the nodular hyperplasia of Cushing syndrome.



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Figure 20-38 Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the lipid content. Mitotic activity and necrosis are not seen.

### *Clinical Features*

The clinical manifestations of primary hyperaldosteronism are those of hypertension and hypokalemia. In the past, aldosterone-producing adenomas were more common, but now, with the widespread use of mineralocorticoid receptor antagonists, they are less common. Conn syndrome occurs most frequently in middle adult life and is more common in women. Aldosterone-producing adenomas account for less than 1% of cases of hypertension, but it is important to recognize because it is a surgically correctable form of hypertension. Primary adrenal hyperplasia associated with hyperaldosteronism is a rare cause of hypertension.

a surgically correctable form of hypertension. Primary adrenal hyperplasia associated with hyperandrogenism occurs more often in children and young adults than in older adults; surgical intervention is not very beneficial in these cases and is best managed with medical therapy with an aldosterone antagonist such as **spironolactone**<sup>®</sup>. The treatment rests on correcting the underlying cause of the stimulation of the renin-angiotensin system.

## Adrenogenital Syndromes

Excess of androgens may be caused by a number of diseases, including primary gonadal disorders. The adrenal cortex secretes two compounds—dehydroepiandrosterone and androstenedione—which are converted to androgens in peripheral tissues for their androgenic effects. Unlike gonadal androgens, adrenal androgen formation and excessive secretion can occur either as a "pure" syndrome or as a component of Cushing disease. Disorders of androgen excess include *adrenocortical neoplasms* and an uncommon group of disorders collectively designated as *adrenogenital syndromes (CAH)*. Adrenocortical neoplasms associated with symptoms of androgen excess (*virilization*) are called *adrenocortical adenomas*. They are morphologically identical to other functional or nonfunctional cortical neoplasms.

CAHs represent a group of autosomal recessive disorders, each characterized by a hereditary defect in steroid biosynthesis, particularly cortisol. In these conditions, decreased cortisol production results in increased secretion due to absence of feedback inhibition. The resultant adrenal hyperplasia causes increased secretion of androgens, which are then channeled into synthesis of androgens with virilizing activity. Certain enzyme defects, adding salt loss to the virilizing syndrome. The most common enzymatic defect in CAH is 21-hydroxylase deficiency, which accounts for more than 90% of cases. 21-Hydroxylase deficiency may range from a total lack to a partial deficiency due to an underlying mutation involving the *CYP21B* gene, which encodes this enzyme.

### Morphology

In all cases of CAH, the adrenals are **hyperplastic bilaterally**, sometimes expanding to many times normal weights, because of the sustained elevation in ACTH. The adrenal cortex is thickened, and on cut section, the widened cortex appears brown as a result of depletion of lipid. The cells are mostly compact, eosinophilic, lipid-depleted cells, intermixed with lipid-laden cells. In addition to cortical abnormalities, **adrenomedullary dysplasia** has also been recently reported in association with salt-losing 21-hydroxylase deficiency. The medullary dysplasia is characterized by displacement of chromaffin cells to the center of the gland, with pronounced intermingling of neuroendocrine cells with cortical cells in the periphery. Hyperplasia of corticotroph (ACTH-producing) cells in the anterior pituitary in most patients.

### Clinical Features

The clinical manifestations of CAH are determined by the specific enzyme deficiency and include hypoadrenalism, sodium homeostasis, and (in severe cases) glucocorticoid deficiency. Depending on the specific defect, the onset of clinical symptoms may occur in the perinatal period, later childhood, or (less commonly) in adulthood.

In 21-hydroxylase deficiency, *excessive androgenic activity* causes signs of masculinization in females and pseudo-hermaphroditism in infants to oligomenorrhea, hirsutism, and acne in postpubertal females. In some forms of CAH (e.g., 11 $\beta$ -hydroxylase deficiency), the androgen excess is associated with enlargement of the external genitalia and other evidence of precocious puberty in females and oligospermia in older individuals. In some forms of CAH (e.g., 11 $\beta$ -hydroxylase deficiency), the androgen excess is associated with increased mineralocorticoid activity, with resultant *sodium retention* and *hypertension*. In other cases, however, with 21-hydroxylase deficiency, the enzymatic defect is severe enough to produce mineralocorticoid *wasting*. Cortisol deficiency places individuals with CAH at risk for *acute adrenal insufficiency* (dis

CAH should be suspected in any neonate with ambiguous genitalia; severe enzyme deficiency in males, with vomiting, dehydration, and salt wasting. In the milder variants, females may present with oligomenorrhea, or hirsutism. In all such cases, an androgen-producing ovarian neoplasm must be excluded. Both adrenal hyperplasia and adrenal neoplasms are treated with exogenous glucocorticoids, which, in addition to providing adrenal suppression, suppress ACTH levels and thus decrease the excessive synthesis of the steroid hormones responsible for the abnormalities.

## SUMMARY

**Adrenogenital Syndromes** The adrenal cortex can secrete excess androgens. Adrenocortical neoplasms (usually "virilizing" carcinomas) or congenital adrenal hyperplasia (CAH). CAH is a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually cortisol; the common subtype is caused by deficiency of 21-hydroxylase. Reduction in cortisol production causes a compensatory increase in androgen production, which in turn stimulates androgen production. Androgens have virilizing effects, leading to masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism) and in some instances, salt (sodium) wasting and hypotension. There are also cases of adrenomedullary dysplasia, a subset of 21-hydroxylase-deficient patients also affected by adrenomedullary dysplasia.



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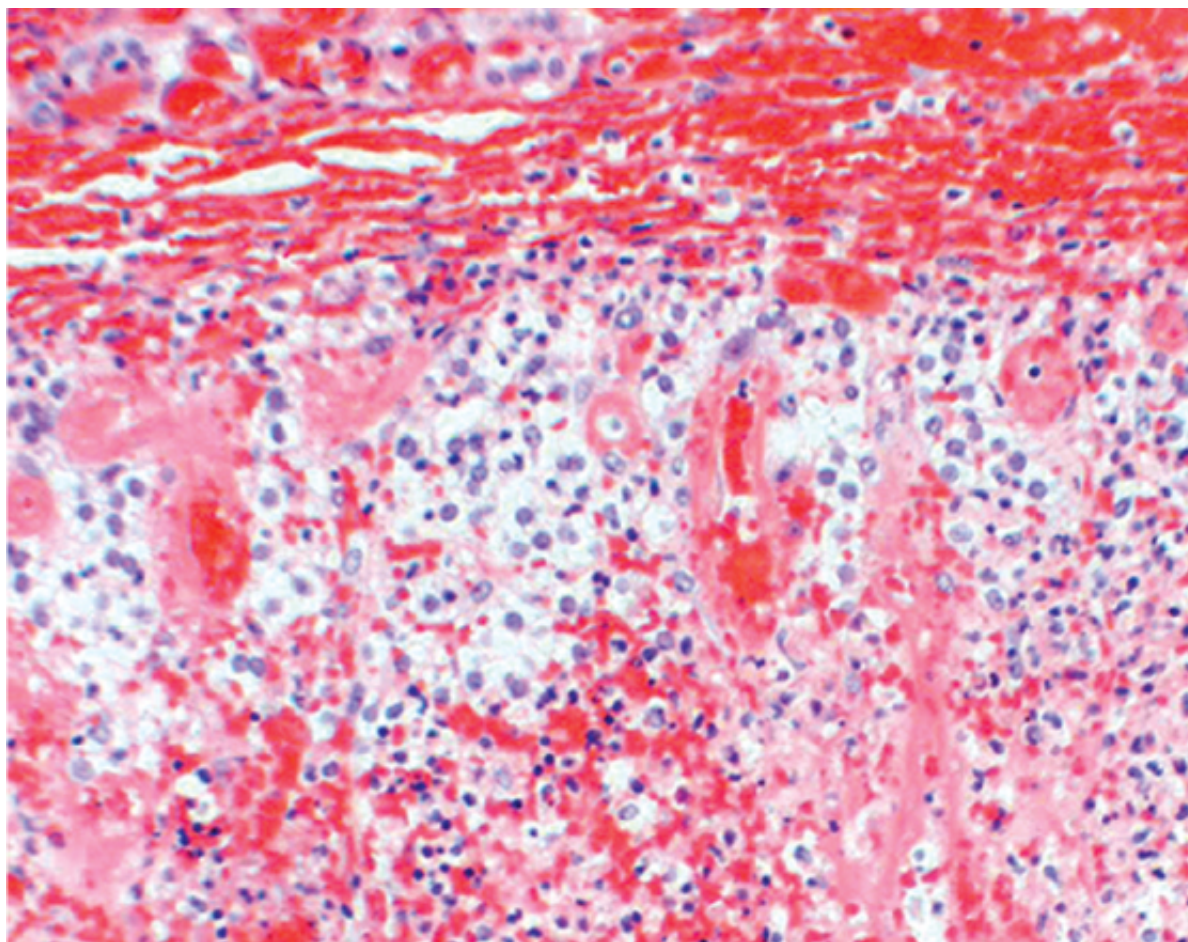
## ADRENAL INSUFFICIENCY

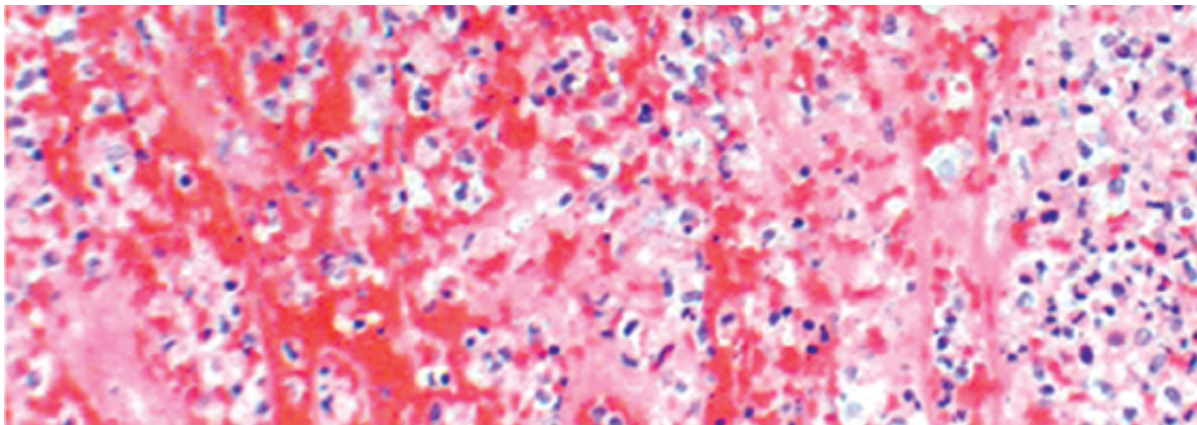
Adrenocortical insufficiency, or hypofunction, may be caused by either primary adrenal disease (p stimulation of the adrenals resulting from a deficiency of ACTH (secondary hypoadrenalism). The can be considered under the following headings: (1) primary *acute* adrenocortical insufficiency (ac adrenocortical insufficiency (*Addison disease*), and (3) secondary adrenocortical insufficiency.

### Acute Adrenocortical Insufficiency

Acute adrenocortical insufficiency occurs most commonly in the clinical settings listed in [Table 20. insufficiency may develop an acute crisis after any stress that taxes their limited physiologic reser corticosteroids, rapid withdrawal of steroids or failure to increase steroid doses in response to an adrenal crisis, because of the inability of the atrophic adrenals to produce glucocorticoid hormone destroy the adrenal cortex sufficiently to cause acute adrenocortical insufficiency. This condition n anticoagulant therapy, in postoperative patients who develop disseminated intravascular coagulat suffering from overwhelming sepsis \(Waterhouse-Friderichsen syndrome\) \(\[Fig. 20-39\]\(#\)\). This catas associated with \*Neisseria meningitidis\* septicemia but can also be caused by other organisms, inc pneumococci, and \*Haemophilus influenzae\*. The pathogenesis of the Waterhouse-Friderichsen sy involves endotoxin-induced vascular injury with associated disseminated intravascular coagulation](#)

### Chronic Adrenocortical Insufficiency (Addison Disease)





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Figure 20-39 Acute adrenal insufficiency caused by severe bilateral adrenal hemorrhage in an infant with over syndrome). At autopsy the adrenals were grossly hemorrhagic and shrunk; microscopically, little resic

Addison disease, or chronic adrenocortical insufficiency, is an uncommon disorder resulting from cortex. More than 90% of all cases are attributable to one of four disorders: *autoimmune adrenalitis* (AIDS) or *metastatic cancers* (Table 20-7).

*Autoimmune adrenalitis* accounts for 60% to 70% of cases and is by far the most common developed countries. As the name implies, there is autoimmune destruction of steroid-prod key steroidogenic enzymes have been detected in these patients. In about half of the patie restricted to the adrenal glands (*isolated autoimmune Addison disease*); in the remaining p such as Hashimoto disease, pernicious anemia, type I diabetes mellitus, and idiopathic hyp *polyendocrinopathy syndrome*). A subset of autoimmune polyendocrinopathy syndrome is autoimmune regulator 1 (*AIRE1*) gene on chromosome 21q22. *Infections*, particularly tuber also cause primary chronic adrenocortical insufficiency. Tuberculous adrenalitis, which onc cases of Addison disease, has become less common with the advent of antituberculous the tuberculosis in many urban centers, this cause of adrenal deficiency must be borne in mind is usually associated with active infection in other sites, particularly the lungs and genitouri infections caused by *Histoplasma capsulatum* and *Coccidioides immitis* may also result in Patients with AIDS are at risk for developing adrenal insufficiency from several infectious (*intracellulare*) and noninfectious (Kaposi sarcoma) complications of their disease. *Metastati* another potential cause of adrenal insufficiency. The adrenals are a fairly common site for carcinomas. Although adrenal function is preserved in most such patients, the metastatic g adrenal cortex to produce a degree of adrenal insufficiency. Carcinomas of the lung and br metastases in the adrenals, although many other neoplasms, including gastrointestinal car hematopoietic neoplasms, may also metastasize to the organ.

**Table 20-7. Causes of Adrenal Insufficiency**

<b>Acute</b>
Waterhouse-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency
<b>Chronic</b>
<b>MAJOR CONTRIBUTORS</b>
Autoimmune adrenalitis
Tuberculosis
Acquired immunodeficiency syndrome
Metastatic disease

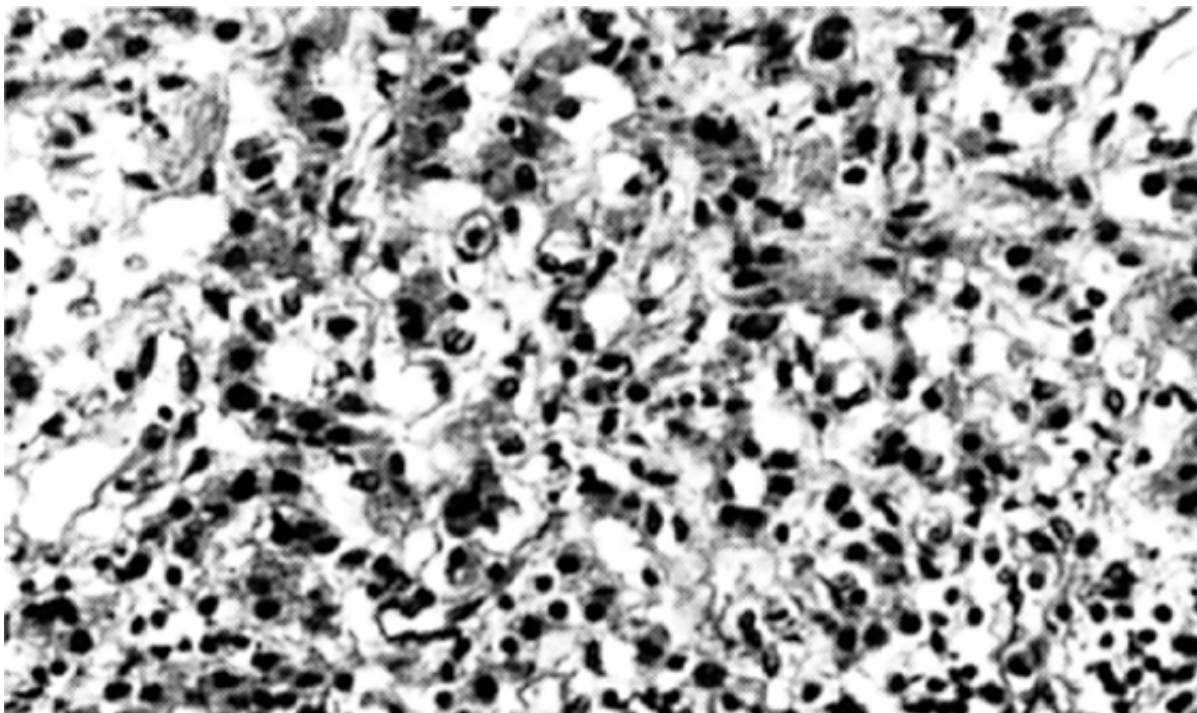
<b>MINOR CONTRIBUTORS</b>
Systemic amyloidosis
Fungal infections
Hemochromatosis
Sarcoidosis

### Secondary Adrenocortical Insufficiency

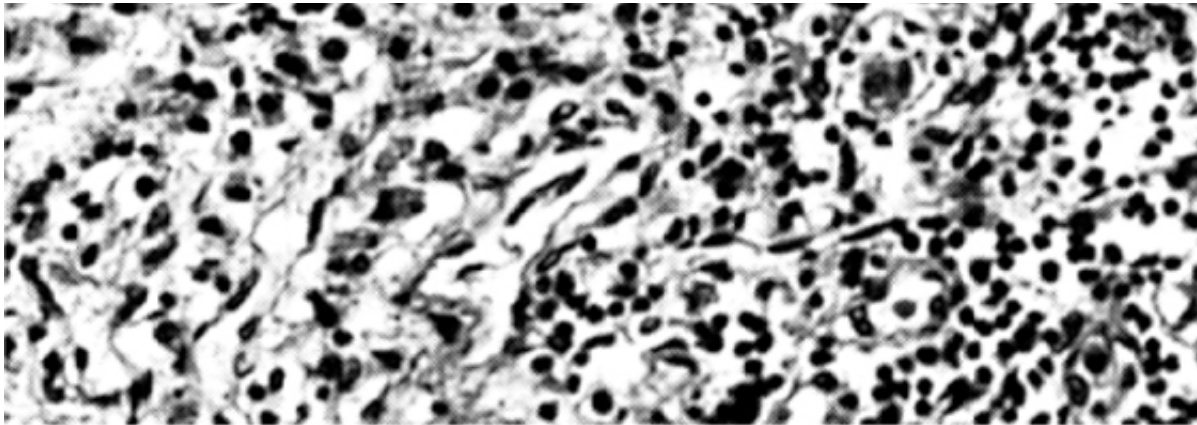
Any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or ACTH leads to a syndrome of hypoadrenalism having many similarities to Addison disease. With : hyperpigmentation of primary Addison disease is lacking because melanotropic hormone levels are low but in some instances, it is only one part of panhypopituitarism, associated with multiple tropic hormone deficiencies. In primary disease, serum ACTH levels may be normal, but the destruction of the adrenal cortex does not respond to administered ACTH in the form of increased plasma levels of cortisol. By contrast, secondary adrenal insufficiency is characterized by low serum ACTH and a prompt rise in plasma cortisol levels in response to ACTH administration.

#### Morphology

The appearance of the adrenal glands varies with the cause of the adrenocortical insufficiency. In **hypoadrenalism** the adrenals are reduced to small, flattened structures that usually lack a capsule because of a small amount of residual lipid. A uniform, thin rim of atrophic yellow cortex surrounds an intact medulla. Histologically, there is atrophy of cortical cells with loss of cytoplasmic lipid in the zona fasciculata and reticularis. **Primary** autoimmune adrenalitis is characterized by lymphocytic infiltration of the adrenal glands, which may be exceedingly difficult to identify within the suprarenal adipose tissue. The cortex contains only scattered residual cortical cells in a collapsed network of connective tissue. A lymphoid infiltrate is present in the cortex and may extend into the subjacent medulla. The medulla is otherwise preserved. In cases of **tuberculosis or fungal diseases** the adrenal glands are effaced by a granulomatous inflammatory reaction identical to that encountered in other organs. Demonstration of the responsible organism may require the use of special stains. In cases caused by **metastatic carcinoma**, the adrenals are enlarged and their normal architecture is replaced by the infiltrating neoplasm.







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 Figure 20-40 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is

### Clinical Features

In general, clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the gland is compromised. The initial manifestations often include progressive weakness and easy fatigability, weight loss, and other nonspecific complaints. *Gastrointestinal disturbances* are common and include anorexia, nausea, vomiting, and abdominal pain. With primary adrenal disease, increased levels of ACTH precursor hormone stimulate melanocyte-stimulating hormone (MSH) receptors on skin and mucosal surfaces. The face, axillae, nipples, areolae, and perineum are particularly common sites of hyperpigmentation. In contrast, hyperpigmentation is not seen in individuals with secondary adrenocortical insufficiency. Hypotension (aldosterone) activity in patients with primary adrenal insufficiency results in potassium retention and hyponatremia, volume depletion, and hypotension; in contrast, secondary hypoadrenalism results in decreased cortisol and androgen output but normal or near-normal aldosterone synthesis. Hypoglycemia may result from glucocorticoid deficiency and impaired gluconeogenesis. Stresses such as infections, trauma, or surgery may precipitate an acute adrenal crisis, manifested by intractable vomiting, abdominal pain, hypotension, and shock, which follows rapidly unless corticosteroids are replaced immediately.

### SUMMARY

**Adrenocortical Insufficiency (Hypoadrenalism)** Primary adrenocortical insufficiency (Waterhouse-Friderichsen syndrome) or chronic (Addison disease) Chronic adrenocortical insufficiency is most often secondary to autoimmune adrenalitis, which may be part of an autoimmune polyglandular syndrome. Tuberculosis and opportunistic infections associated with the human immunodeficiency virus, and tumors metastatic to the adrenal gland are other important causes of chronic hypoadrenalism. Patients typically present with weakness, weight loss, and gastrointestinal disturbances. Primary adrenocortical insufficiency is also characterized by elevated ACTH levels with associated skin pigmentation.







## ADRENOCORTICAL NEOPLASMS



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Figure 20-41 Adrenal carcinoma. The bright yellow tumor dwarfs the kidney and compresses the upper pole

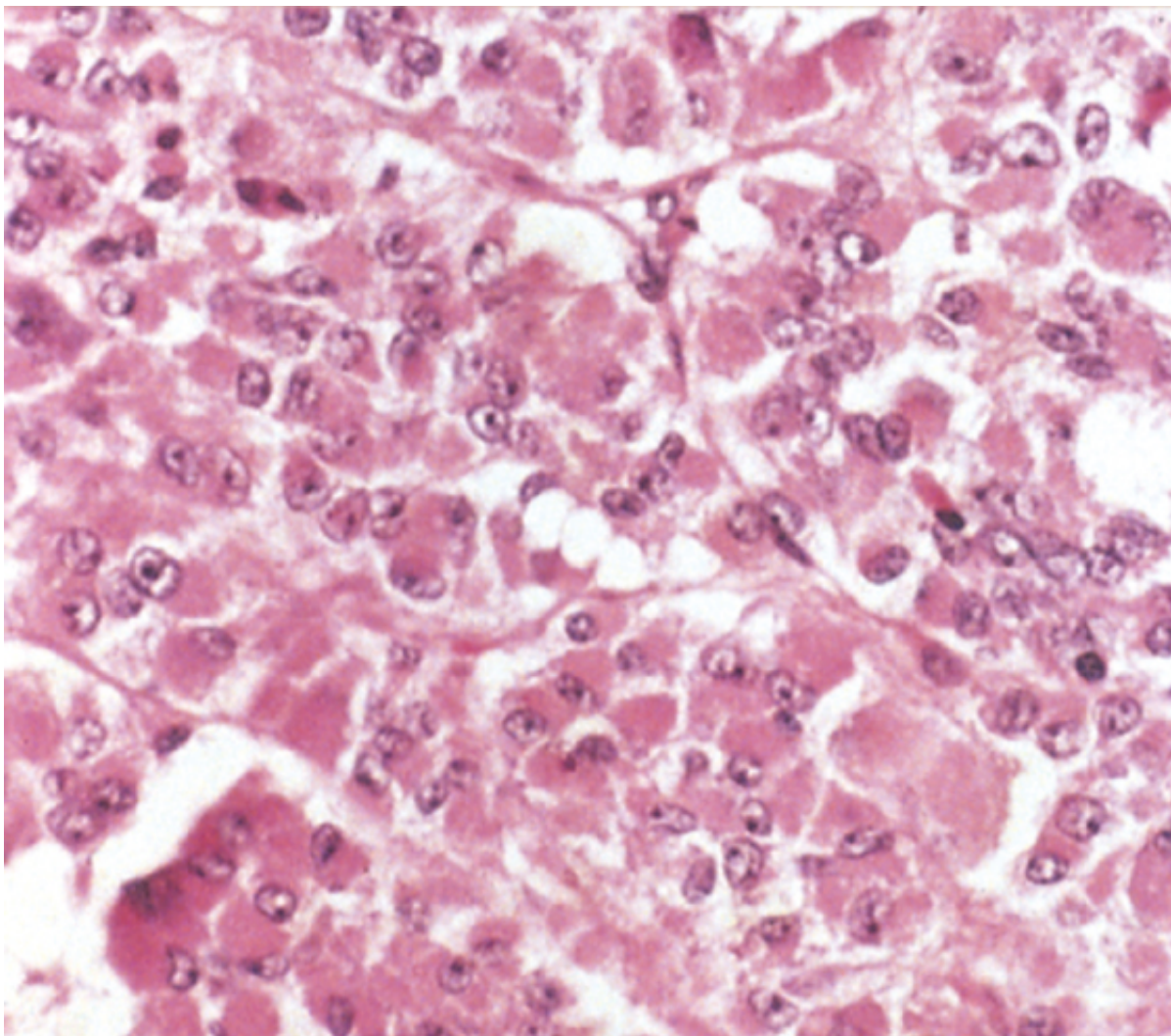
It should be evident from the discussion of adrenocortical hyperfunction that functional adrenal neoplasms are associated with the various forms of hyperadrenalism. While functional adenomas are most commonly associated with Cushing syndrome, a virilizing neoplasm is more likely to be a carcinoma. However, not all adrenal neoplasms produce hormones. Determination of whether a cortical neoplasm is functional or not is based on clinical evidence of hormone excess or its metabolites in the laboratory. In other words, *functional and nonfunctional adrenocortical neoplasms are distinguished on the basis of morphologic features.*

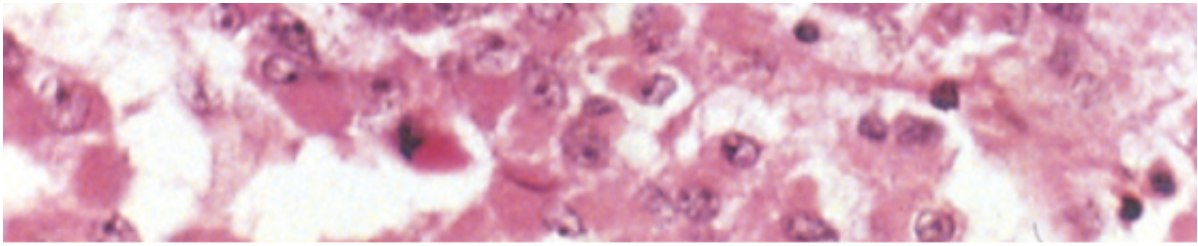
### Morphology

**Adrenocortical adenomas** were described in the earlier discussions of Cushing's syndrome.

hyperaldosteronism. Most cortical adenomas do not cause hyperfunction and are usually incidental findings at the time of autopsy or during abdominal imaging for an unrelated condition. The half-jocular, half-facetious appellation of "**adrenal incidentaloma**" has crept into the medical literature for these incidentally discovered tumors. On cut surface, adenomas are usually yellow to yellow-tan, reflecting the presence of lipid within the neoplastic cells (see Fig. 20-37). As a general rule they are less than 2 cm in diameter. Microscopically, adenomas are composed of cells similar to those of the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism is seen even in benign lesions ("endocrine atypia") (see Fig. 20-38). The cytoplasm of the cells may range from eosinophilic to vacuolated, depending on their lipid content; mitotic activity is rare.

**Adrenocortical carcinomas** are rare neoplasms that may occur at any age, including children. Known inherited causes of adrenocortical carcinomas include the Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome (Chapter 7). In most cases, adrenocortical carcinomas are large, invasive lesions that efface the native adrenal gland. On cut surface, adrenocortical carcinomas are large, variegated, poorly demarcated lesions containing areas of necrosis, hemorrhage, and calcification (Fig. 20-41). Microscopically, adrenocortical carcinomas may be composed of well-differentiated cells similar to those seen in cortical adenomas or bizarre, pleomorphic cells, which may be difficult to distinguish from an undifferentiated carcinoma metastatic to the adrenal (Fig. 20-42). Adrenal carcinomas have a tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional lymph nodes and distant organs are common, as are distant hematogenous spread to the lungs and other viscera. The prognosis is poor. The median patient survival is about 2 years.





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Figure 20-42 Adrenal carcinoma with marked anaplasia.



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## ADRENAL MEDULLA

The adrenal medulla is embryologically, functionally, and structurally distinct from the adrenal cortex. It is populated by cells derived from the neural crest (*chromaffin* cells) and their supporting (sustentacular) cells. The chromaffin cells, so named because of their brown-black color after exposure to potassium dichromate, synthesize and secrete catecholamines in response to signals from preganglionic nerve fibers in the sympathetic nervous system. Similar collections of cells are distributed throughout the body in the extra-adrenal paraganglion system. The most important diseases of the adrenal medulla are neoplasms, which include both neuronal neoplasms (including neuroblastomas and more mature ganglion cell tumors) and neoplasms composed of chromaffin cells (pheochromocytomas).







## PHEOCHROMOCYTOMA

Pheochromocytomas are neoplasms composed of chromaffin cells, which, like their non-neoplastic counterparts, secrete catecholamines and, in some cases, other peptide hormones. These tumors are of special importance because they (like aldosterone-secreting adenomas) give rise to a surgically correctable form of hypertension.

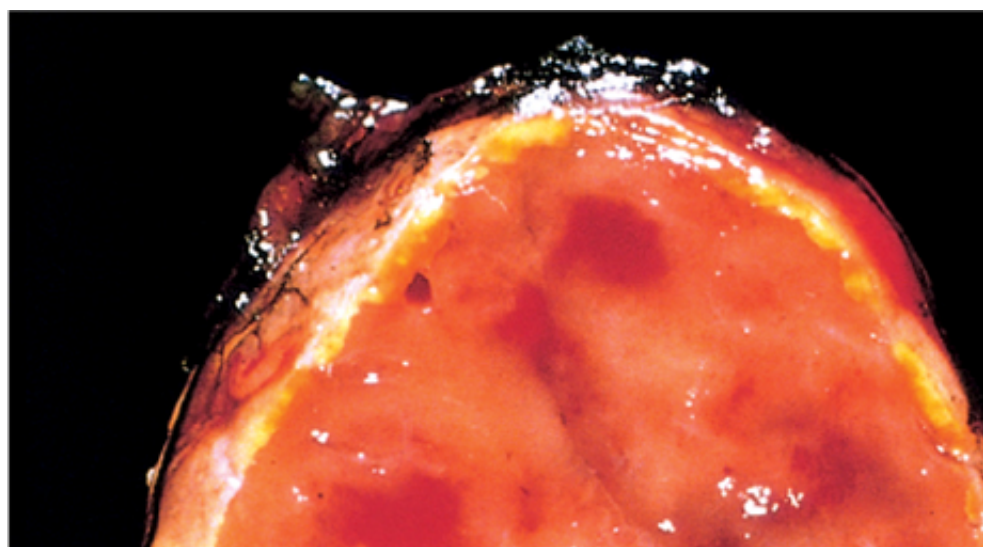
Pheochromocytomas usually subscribe to a convenient "rule of 10s":

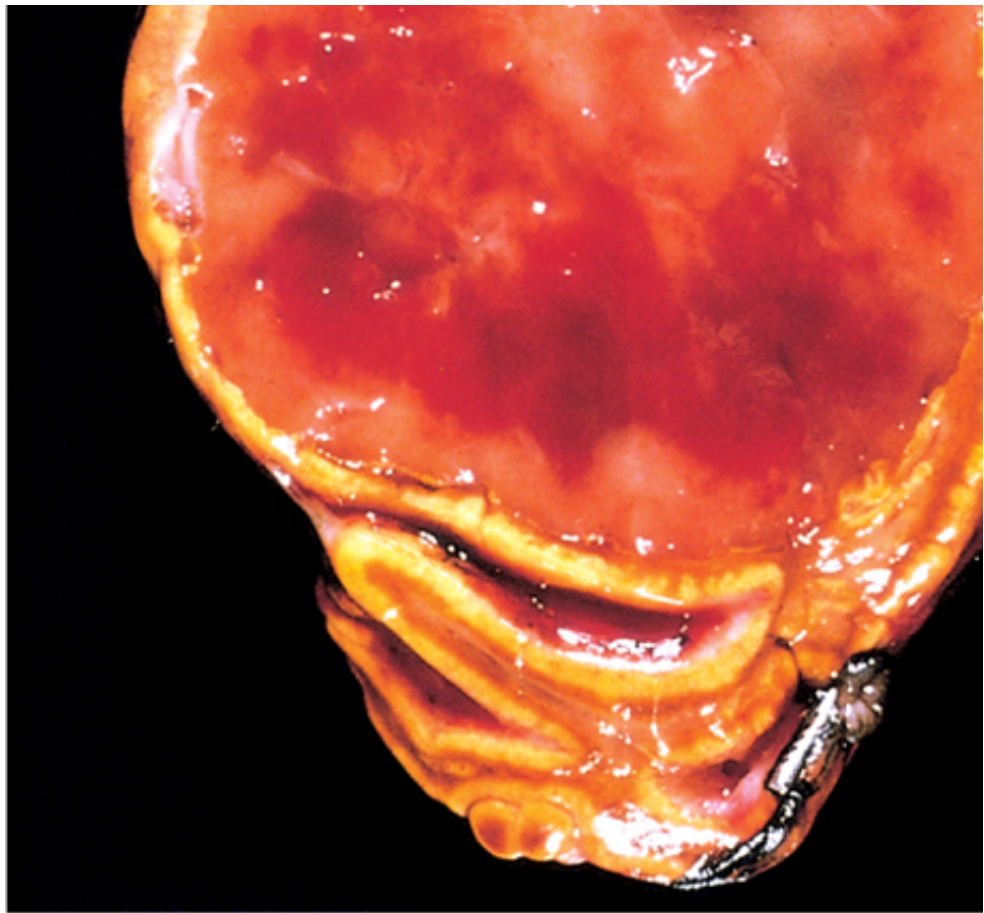
*10% of pheochromocytomas arise in association with one of several familial syndromes. These include the von Hippel-Lindau syndrome (described later), type 1 neurofibromatosis (Chapter 23), von Hippel-Lindau disease, and the carotid body, where they are usually called paragangliomas rather than pheochromocytomas. 10% of pheochromocytomas are extra-adrenal, occurring in the sympathetic chain and the carotid body, where they are usually called paragangliomas rather than pheochromocytomas. 10% of pheochromocytomas are bilateral; this figure may rise to 50% in cases that are associated with a hereditary syndrome. 10% of pheochromocytomas are biologically malignant, although the associated hypertension represents a complication of even "benign" tumors. Frank malignancy is somewhat more common in tumors of the sympathetic chain.*

### Morphology

Pheochromocytomas range from small, circumscribed lesions confined to the adrenal medulla to large, invasive masses weighing several kilograms. On cut surface, smaller pheochromocytomas appear as well-circumscribed, tan to reddish-brown masses that compress the adjacent adrenal cortex (Fig. 20-43). Larger lesions tend to be necrotic, and cystic and typically efface the adrenal gland. Incubation of the fresh tumor in formalin or dichromate solutions turns the tumor a dark brown color, as noted previously.

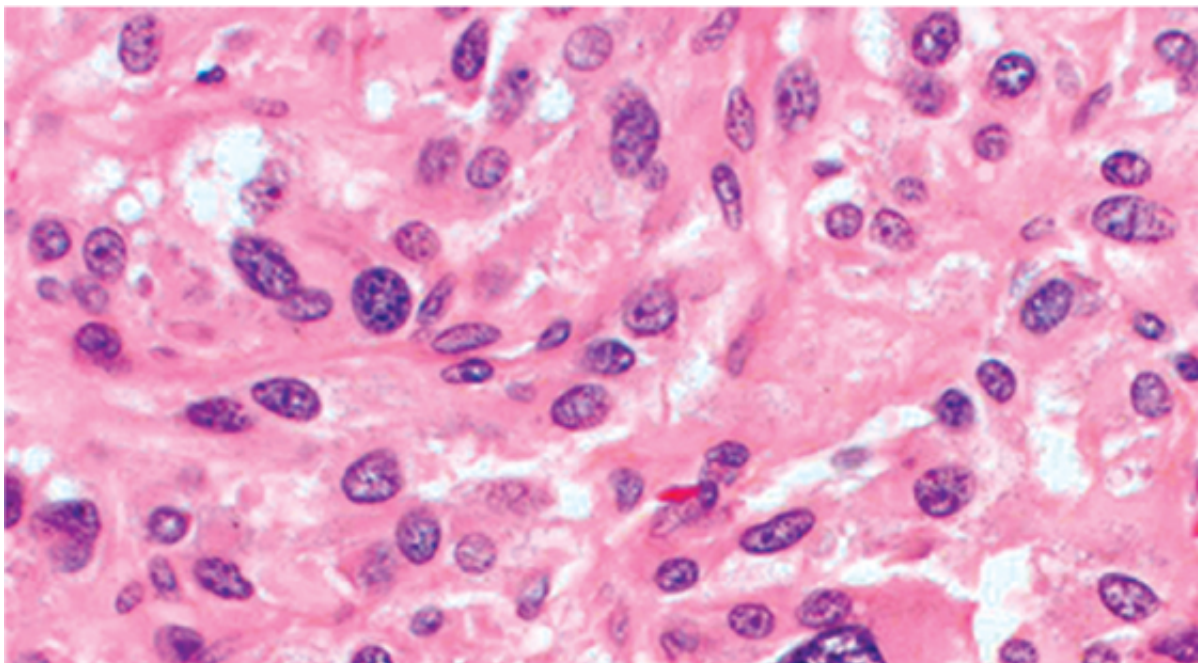
Microscopically, pheochromocytomas are composed of polygonal to spindle-shaped cells, often arranged in nests or "zellballen," by a rich vascular stroma (Fig. 20-44). The cytoplasm of the neoplastic cells often has a finely granular appearance, and the nuclei are often quite pleomorphic. The presence of membrane-bound, electron-dense granules, representing catecholamine granules, is characteristic. Sometimes other peptides are present. The nuclei of the neoplastic cells are often quite pleomorphic. Vascular invasion may be encountered in benign lesions, and the presence of mitoses may imply malignancy. **Therefore, the definitive diagnosis of malignancy in pheochromocytoma is based exclusively on the presence of metastases.** These may involve regional lymph nodes and distant sites, including liver, lung, and bone.

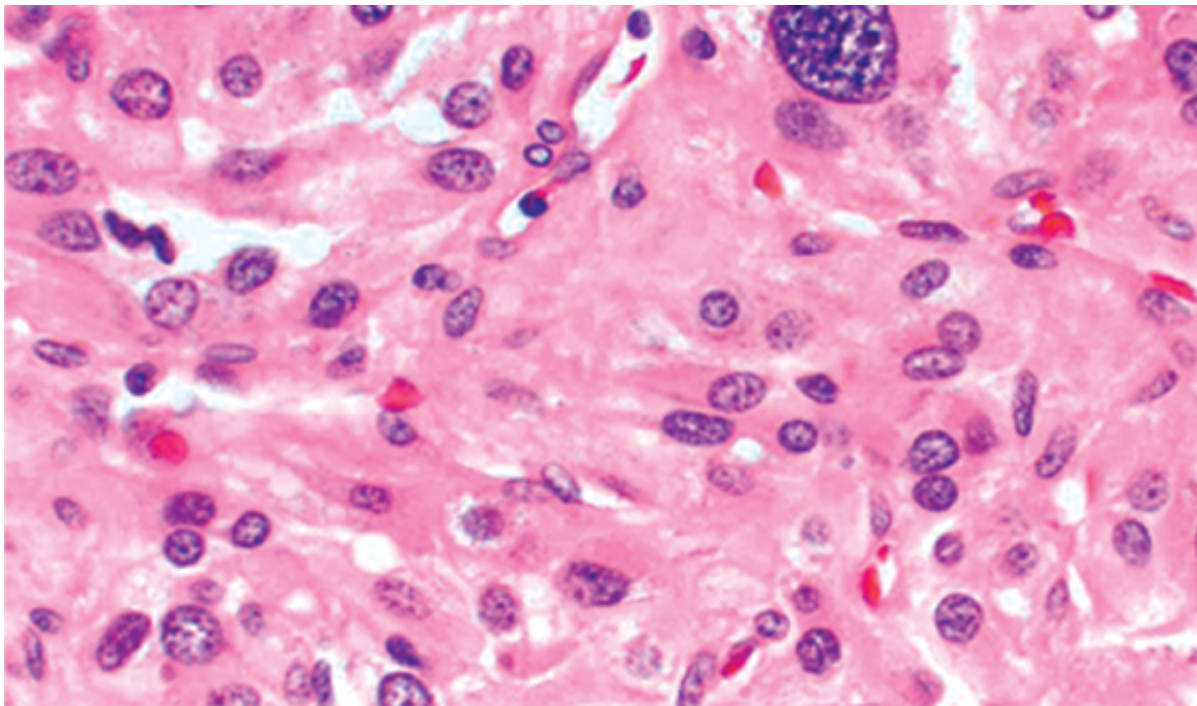




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Figure 20-43 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The histology is seen below.

### *Clinical Features*





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Figure 20-44 Photomicrograph of pheochromocytoma, demonstrating characteristic nests of cells ("Zellballen"). Catecholamine granules are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytoma, but this by itself should not be used to diagnose malignancy.

The dominant clinical manifestation of pheochromocytoma is *hypertension*. Classically, this is described as a sustained elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of anxiety. It may also be associated with pain in the abdomen or chest, nausea, and vomiting. In practice, *isolated hypertension occurs in fewer than half of individuals* with pheochromocytoma. In about two-thirds of cases, the hypertension is sustained or episodic, although an element of labile hypertension may also be present. The hypertension is associated with an increased risk of myocardial ischemia and cerebrovascular accidents. Sudden cardiac death may occur, probably secondary to catecholamine-induced ventricular arrhythmias. In some cases, pheochromocytomas secrete other hormones such as ACTH, which may be associated with clinical features related to the secretion of these and other peptide hormones. The diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines, vanillylmandelic acid, and metanephrines. Isolated benign pheochromocytomas are treated with surgical resection. Intraoperative medication of patients with adrenergic-blocking agents. Multifocal lesions may require more extensive surgery.



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## NEUROBLASTOMA AND OTHER NEURONAL NEOPLASMS

Neuroblastoma is the most common extra-cranial solid tumor of childhood. These neoplasms occur most commonly during the first 5 years of life and may arise during infancy.

Neuroblastomas may occur anywhere in the sympathetic nervous system and occasionally within the brain, but they are most common in the abdomen; most cases arise in either the adrenal medulla or the retroperitoneal sympathetic ganglia. Most neuroblastomas are sporadic, although familial cases also occur. These tumors are discussed in [Chapter 7](#), along with other pediatric neoplasms.







## MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

The MEN syndromes are a group of inherited diseases resulting in proliferative lesions (hyperplasias, adenomas, and carcinomas) of multiple endocrine organs. Like other inherited cancer disorders ([Chapter 6](#)), endocrine tumors arising in the context of MEN syndromes have certain distinctive features that contrast with their sporadic counterparts:

These tumors occur at a *younger age* than sporadic cancers. They arise in *multiple endocrine organs*, either *synchronously* or *metachronously*. Even in one organ, the tumors are often *multifocal*. The tumors are usually preceded by an *asymptomatic stage of endocrine hyperplasia* involving the cell of origin of the tumor (for example, patients with MEN-1 syndrome develop varying degrees of islet cell hyperplasia, some of which progress to pancreatic tumors). These tumors are usually *more aggressive* and *recur* in a higher proportion of cases than similar endocrine tumors that occur sporadically.

Unraveling the genetic basis of the MEN syndromes and applying the knowledge to therapeutic decision making has been one of the success stories of translational research. The salient features of the MEN syndromes are discussed below.





## MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

MEN type 1 is inherited in an autosomal dominant pattern. The gene (*MEN1*) is located at 11q13 and is a tumor suppressor gene; thus, inactivation of both alleles of the gene is believed to be the basis of tumorigenesis. Organs commonly involved include the parathyroid (95%), pancreas (~40%), and pituitary (~30%)-the "3 Ps."

*Parathyroid:* Primary hyperparathyroidism, arising from multiglandular parathyroid hyperplasia, is the most consistent feature of MEN-1. *Pancreas:* Endocrine tumors of the pancreas are the leading cause of death in MEN-1. These tumors are usually aggressive and present with metastatic disease or multifocality. Pancreatic endocrine tumors are often functional (i.e., they secrete hormones). Zollinger-Ellison syndrome, associated with gastrinomas, and hypoglycemia, related to insulinomas, are common endocrine manifestations. *Pituitary:* The most frequent pituitary tumor in MEN-1 patients is a prolactin-secreting macroadenoma. Some individuals develop acromegaly from somatotrophin-secreting tumors.





## MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

MEN type 2 is actually two distinct groups of disorders that are unified by the occurrence of activating mutations of the *RET* protooncogene. There is a strong *genotype-phenotype correlation* within the MEN-2 syndrome, and differences in mutation patterns possibly account for the variable features in the two subtypes. MEN-2 is inherited in an autosomal dominant pattern. The *RET* proto-oncogene is located at 10q11.2.

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### Multiple Endocrine Neoplasia, Type 2A

Organs commonly involved include:

*Thyroid:* Medullary carcinoma of the thyroid develops in virtually all untreated cases, and the tumors usually occur in the first 2 decades of life. The tumors are commonly multifocal, and foci of C-cell hyperplasia can be found in the adjacent thyroid. *Adrenal medulla:* 50% of patients develop adrenal pheochromocytomas; fortunately, no more than 10% are malignant. *Parathyroid:* Approximately a third of patients develop parathyroid gland hyperplasia with primary hyperparathyroidism.

### Multiple Endocrine Neoplasia, Type 2B

Organs commonly involved include the thyroid and adrenal medulla. The spectrum of thyroid and adrenal medullary disease is similar to that in MEN-2A. *However, unlike MEN-2A, patients with MEN-2B:*

Do not develop primary hyperparathyroidism  
*Develop extraendocrine manifestations:*  
ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue) and marfanoid habitus

Before the advent of genetic testing, family members of individuals with the MEN-2 syndrome were screened with annual biochemical tests, which often lacked sensitivity. Now, routine genetic testing identifies *RET* mutation carriers earlier and more reliably in MEN-2 kindreds; *all persons carrying germ-line RET mutations are advised to have prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas.* Surgical intervention based on the results of a single genetic test represents a new paradigm in the practice of "molecular medicine."

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## 21 The Musculoskeletal System\*

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The musculoskeletal system imparts form and movement to the human body. Aside from providing the fulcrums and levers against which muscles contract to allow movement, the skeleton is critical for mineral (particularly calcium) homeostasis, and also protects viscera and supplies an environment conducive to both hematopoietic and mesenchymal stem cell development. The term *musculoskeletal disease* embraces a large number of conditions ranging from localized, benign lesions of the bone such as the osteochondroma to generalized disorders such as osteoporosis, osteogenesis imperfecta, and muscular dystrophy. In this chapter we will first consider some of the more common conditions affecting the bones and joints, then discuss selected diseases of skeletal muscle, concluding with a brief commentary about tumors arising in the various soft tissues of the body.



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## BONES

### CONGENITAL DISEASES OF BONE

Congenital diseases of bone range from localized malformations to hereditary disorders associated with abnormalities affecting the entire skeletal system. Developmental anomalies resulting from localized problems in the migration of mesenchymal cells and the formation of condensations are called *dysostoses*. They are usually limited to defined embryologic structures and can result from mutations in specific homeobox genes. Some of the more common lesions include *aplasia* (e.g., congenital absence of a digit or rib), the formation of extra bones (e.g., supernumerary digits or ribs), and abnormal fusion of bones (e.g., premature closure of the cranial sutures or congenital fusion of the ribs). Such malformations may occur as isolated, sporadic lesions or as components of a more complex syndrome. Mutations that interfere with bone or cartilage growth and/or maintenance of normal matrix components (e.g. those affecting growth factors or their receptors) have more diffuse effects; such disorders are called *dysplasias*. The number of such disorders (well over 200) renders the discussion of all but the most common impossible in the limited space here. In addition, a number of hereditary metabolic disorders not usually thought of as primary skeletal diseases (e.g., mucopolysaccharidoses like Hurler syndrome) can also affect the bone matrix; such conditions are discussed briefly with other genetic disorders in [Chapter 7](#).

#### Osteogenesis Imperfecta

*Osteogenesis imperfecta (OI)*, also known as "brittle bone disease", is actually a group of hereditary disorders caused by defective synthesis of type I collagen. Because type I collagen is a major component of extracellular matrix in other parts of the body, there are also numerous extraskkeletal manifestations (affecting e.g., skin, joints, and eyes). The molecular pathology underlying OI characteristically involves gene mutations in the coding sequences for  $\alpha_1$  or  $\alpha_2$  chains of type I collagen. Because successful collagen synthesis and extracellular export require formation of a complete and intact triple helix, any primary defect in a collagen chain tends to disrupt the entire structure and results in its premature degradation (an example of a *dominant negative mutation*; see [Chapter 7](#)). As a consequence, most defects manifest as autosomal dominant disorders and can have a disastrous phenotype. There is, however, a broad spectrum of severity, and mutations that result in qualitatively normal collagen but at only reduced levels generally have milder manifestations.

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*The fundamental abnormality in all forms of OI is too little bone*, resulting in extreme skeletal fragility. There are four major subtypes, with an extremely broad range of clinical outcomes. Thus, the type II variant is uniformly fatal pre- or immediately post-partum due to multiple fractures that occur *in utero*. In contrast, patients with type I OI have a normal lifespan, with only a modestly increased proclivity to fractures during childhood (decreasing in frequency after puberty). The classic finding of *blue sclerae* in type I OI is attributable to decreased scleral collagen content; this causes a relative transparency that allows the underlying choroid to be seen. *Hearing loss* can be related to conduction defects in the middle and inner ear bones, and *small misshapen teeth* are a result of dentin deficiency.

#### Achondroplasia

*Achondroplasia is a major cause of dwarfism*. The underlying etiology is a point mutation in the fibroblast growth factor receptor 3 (FGFR3) that results in its constitutive activation. Unfortunately, activated FGFR3 *inhibits* chondrocyte proliferation; as a result, the normal epiphyseal growth plate expansion is suppressed and long bone growth is severely stunted.

Because the most common mutation leads to ligand-independent FGFR3 activation, the disorder is typically autosomal dominant. The affected individuals are typically heterozygotes, since homozygosity leads to abnormalities in chest development and death from respiratory failure soon after birth. Interestingly, four of five cases represent new spontaneous mutations.

Achondroplasia affects all bones that form from a cartilaginous framework. The most conspicuous changes include marked, disproportionate shortening of the proximal extremities, bowing of the legs, and a lordotic (sway-backed) posture. The cartilage growth plates are disorganized and hypoplastic, in contrast to the expanded, orderly columns normally seen at the epiphyses.

*Thanatophoric dwarfism* is a lethal variant of dwarfism, affecting 1 in every 20,000 live births (*thanatophoric* means "death loving"). This disease is also caused by FGFR3 mutations, but involves missense or point mutations in different domains of the receptors, distinct from those in achondroplasia. Affected heterozygotes have extreme shortening of the limbs, frontal bossing of the skull, and an extremely small thorax, which is the cause of fatal respiratory failure in the perinatal period.

### **Osteopetrosis**

*Osteopetrosis is a group of rare genetic disorders characterized by reduced osteoclast-mediated bone resorption and therefore defective bone remodelling. Osteopetrosis* (literally "stone bone") is a seemingly apt name, since the affected bone is grossly dense and stone-like. Paradoxically, the bone is architecturally unsound and fractures as readily as a piece of chalk. There are four variants distinguished on the basis of clinical findings and modes of inheritance.

Bone resorption occurs through osteoclast-driven enzymatic degradation of the proteinaceous bone matrix. However, before the matrix can be digested, it must first be decalcified. This is achieved by osteoclasts tightly applying themselves to the bony surface (at sites called *Howship lacunae*) and sealing their edges to prevent leaks. This is important because the extracellular space between osteoclast and bone becomes functionally analogous to a secondary lysosome. The space is acidified by a proton pump, and the inorganic hydroxyapatite matrix is dissolved. The osteoclast also releases a number of matrix degrading enzymes; as part of the degradative process, mediators that were previously deposited in the matrix (largely by osteoblasts) are also released and become active.

The precise nature of the osteoclast dysfunction is unknown in most cases. Nevertheless, there is a variant associated with *carbonic anhydrase II deficiency* that makes excellent pathogenic sense because this enzyme is required for the osteoclast hydrogen ion excretion and, therefore, for acidification of the site of bone resorption. Thus, defective bone remodeling in these patients is directly attributable to reduced bone demineralization.

Besides fractures, patients with osteopetrosis frequently have cranial nerve problems (due to compression from surrounding bone), and recurrent infections. The latter is attributable to diminished hematopoiesis resulting from reduced marrow space. Indeed, osteopetrotic patients often develop impressive hepatosplenomegaly due to expansive extramedullary hematopoiesis.

Because osteoclasts are derived from marrow monocyte precursors, bone marrow transplants hold the promise of re-populating recipients with progenitors capable of differentiating into fully functional osteoclasts. Indeed, many of the skeletal abnormalities appear to be reversible once normal precursor cells are provided.

### **SUMMARY**

**Congenital Diseases of Bone** Congenital malformations are called *dysostoses* and can result in the absence of bones,

supernumerary bones, or inappropriately fused bones; these are typically due to mutations in homeobox genes affecting localized migration and condensation of primitive mesenchymal cells. Abnormalities in bone organogenesis are called *dysplasias*; these can be caused by mutations in a variety of signal transduction pathways or in components of the extracellular matrix:

Achondroplasia (dwarfism) occurs as a consequence of constitutive FGFR3 activation resulting in defective cartilage synthesis at growth plates. Osteogenesis imperfecta (brittle bone disease) is a group of disorders related to abnormal type I collagen synthesis with resultant bone fragility and susceptibility to fractures. Osteopetrosis results in a dense but architecturally unsound bone due to defective osteoclast-induced bone remodeling.







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## ACQUIRED DISEASES OF BONE DEVELOPMENT

Many nutritional, endocrine, and systemic disorders affect the skeletal system. Nutritional deficiencies of vitamin C (involved in collagen cross-linking; deficiency causes *scurvy*) and vitamin D deficiency causes *rickets* and *osteomalacia*). Both of these are discussed in greater detail with other disorders. Primary and secondary hyperparathyroidism (discussed in [Chapter 20](#)) also cause significant skeletal disease. The major focus of the discussion here will be *osteoporosis*, resulting from a disease, a disease associated with the loss of osteoclast function.

### Osteoporosis

*Osteoporosis is a disease characterized by increased porosity of the skeleton resulting from reduced bone mass, an increase in bone fragility and susceptibility to fractures. The disorder may be localized to a certain part of the skeleton, *osteoporosis of a limb*, or may involve the entire skeleton, as a manifestation of a *metabolic bone disease*, a disease associated with the loss of osteoclast function.*

**Table 21-1. Categories of Generalized Osteoporosis**

<b>Primary</b>
Postmenopausal
Senile
<b>Secondary</b>
<b>ENDOCRINE DISORDERS</b>
Hyperparathyroidism
Hypo or hyperthyroidism
Hypogonadism
Pituitary tumors
Diabetes, type 1
Addison disease
<b>NEOPLASIA</b>
Multiple myeloma
Carcinomatosis
<b>GASTROINTESTINAL DISORDERS</b>
Malnutrition
Malabsorption
Hepatic insufficiency
Vitamin C, D deficiencies
Idiopathic
<b>DISEASE DRUGS</b>
Anticoagulants
Chemotherapy
Corticosteroids
Anticonvulsants
Alcohol
<b>MISCELLANEOUS</b>
Osteogenesis imperfecta
Immobilization



Pulmonary disease
Homocystinuria
Anemia



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Figure 21-1 Osteoporotic vertebral body (*right*) shortened by compression fractures, compared with a normal vertebral body (*left*). Note a characteristic loss of horizontal trabeculae and thickened vertical trabeculae.

The most common forms of osteoporosis are *senile* and *postmenopausal* osteoporosis; senile osteoporosis affects both sexes, while postmenopausal osteoporosis obviously affects only women after menopause. Peak bone mass is attained by age 30, but beginning in the third or fourth decade in both sexes, bone resorption begins to outpace bone formation, averaging 0.7% per year—is a normal biological phenomenon. Such losses generally occur in trabecular bone and are therefore more pronounced in the spine and femoral neck. Hence these individuals with osteoporosis. Clearly, if one begins with a greater bone mass, the effects of gradual bone loss with each cycle of remodeling can be accelerated by the postmenopausal state. Hence the importance of preventing osteoporosis and its complications. Regardless of the underlying cause, the progressive loss of bone mass leads to a resultant increase in the risk of fractures. Roughly a million Americans each year experience a fracture; when the morbidity and mortality associated with osteoporosis-related fractures are taken into account, the economic burden of osteoporosis in the United States exceeds \$14 billion.

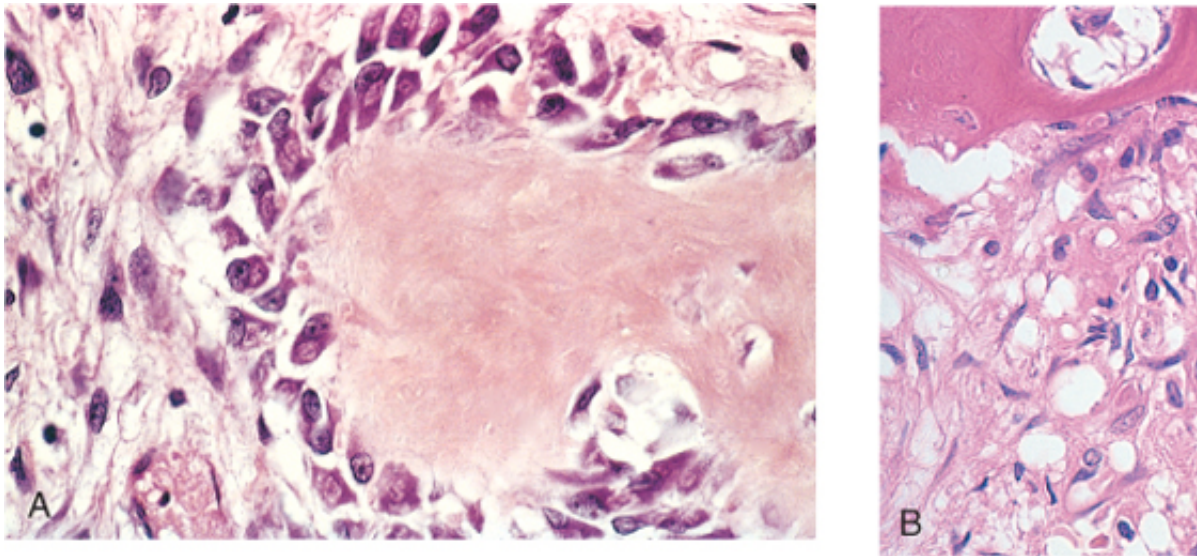
### Morphology

The hallmark of osteoporosis is a loss of bone, which tends to be **most conspicuous in the axial skeleton containing abundant trabecular bone**. The bony trabeculae are thinner and more widely separated than usual, resulting in an increased susceptibility to fractures (Fig. 21-1). In severe osteoporosis, the bone loss is often particularly severe in the vertebral bodies, which may collapse. Similar bone loss is common in other weight-bearing bones, such as the

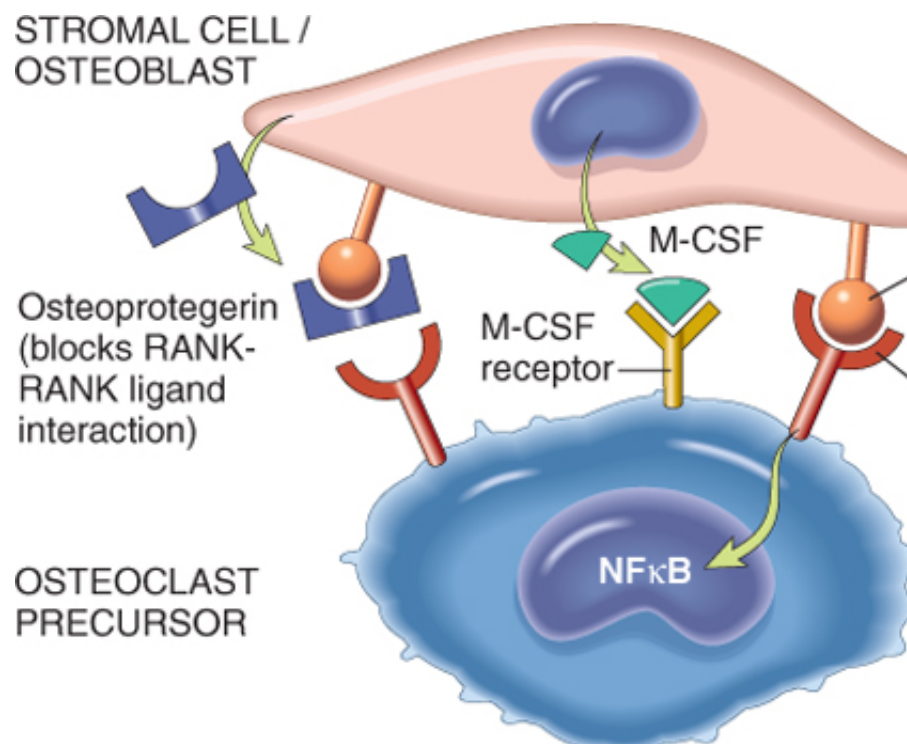
common site for fractures. The major microscopic changes are thinning of the trabeculae and narrowing of the Haversian canals. Osteoclastic activity is present but is not dramatically increased. The remaining bone is normal, and thus there is no alteration in the ratio of mineral to organic matrix.

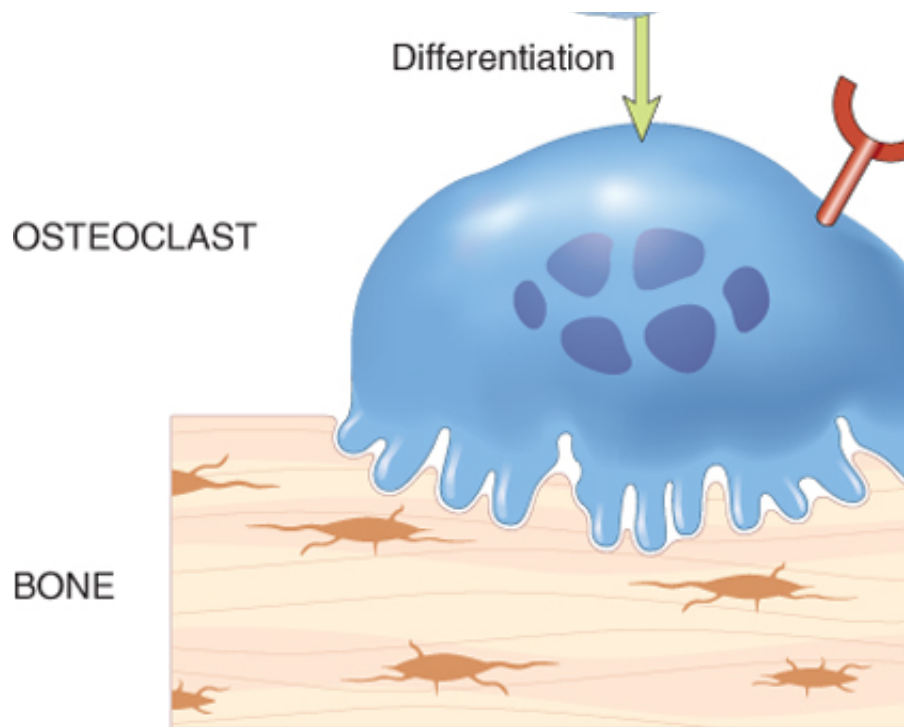
### Pathogenesis

In adults there is a dynamic equilibrium between bone formation by osteoblasts (Fig. 21-2A), mainly osteoclasts (Fig. 21-2B). Osteoporosis occurs when the balance tilts in favor of resorption.



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Figure 21-2 Cells of bone. A, Active osteoblasts synthesizing bone matrix proteins. The surrounding spindle-shaped osteoclasts resorbing bone. The smaller blue nuclei surrounded by a halo of clearing in the dense pink lamellar bone.





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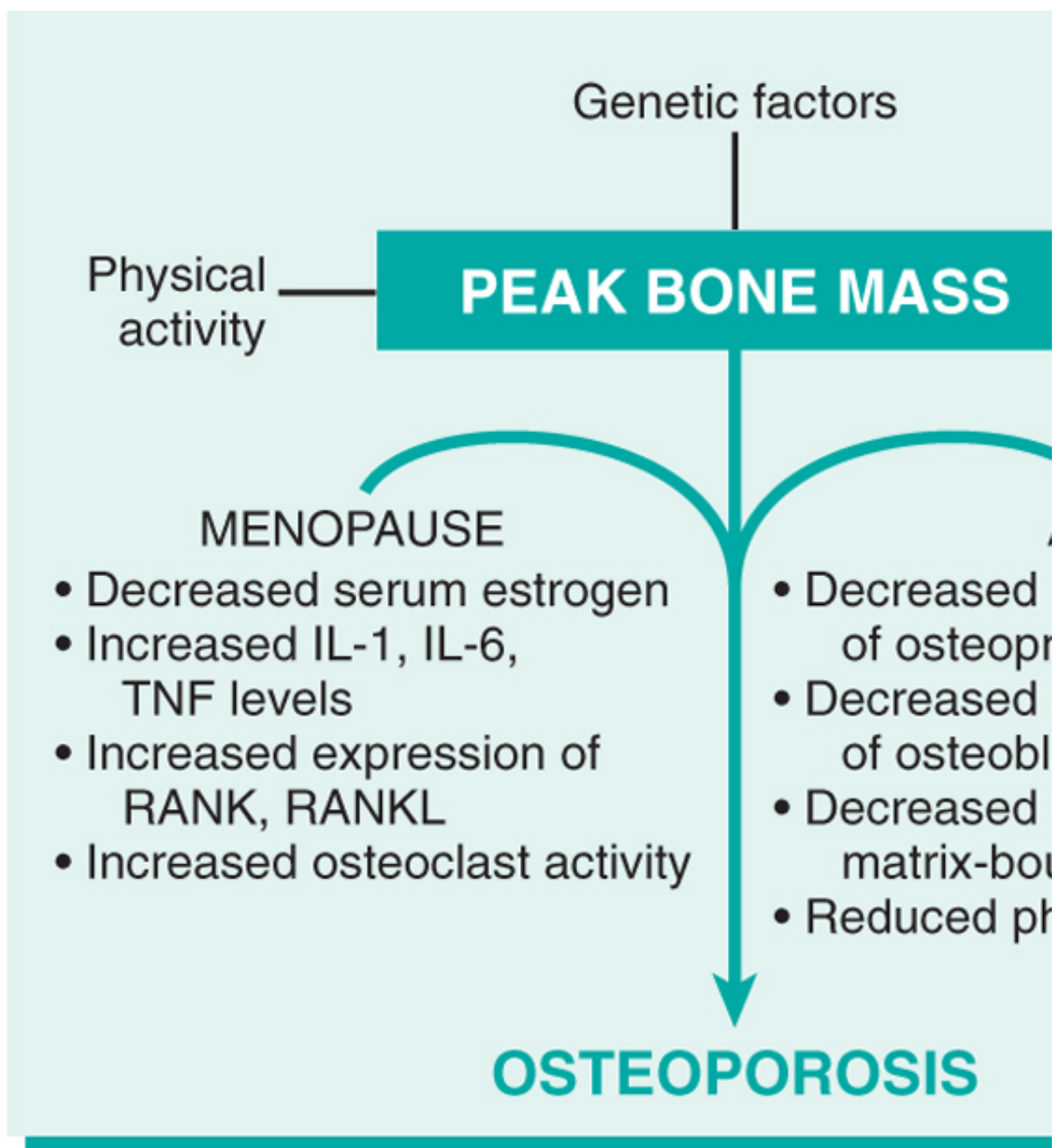
Figure 21-3 Paracrine mechanisms regulating osteoclast formation and function. Osteoclasts are derived from the RANK (receptor activator for nuclear factor- $\kappa$ B) receptors on osteoclast precursors bind RANK ligand (RANKL) expressed by osteoblasts. Along with macrophage colony-stimulating factor (M-CSF), the RANK-RANKL interaction drives the differentiation of osteoclast precursors into osteoclasts. Osteoclasts secrete osteoprotegerin (OPG) that acts as a decoy receptor for RANKL, preventing it from binding the RANK receptor. This prevents bone resorption by inhibiting osteoclast differentiation.

Although a complete understanding of the underlying control mechanisms of bone remodeling is rare, exciting new insights. Central to these is the recognition that novel members of the tumor necrosis factor (TNF) family regulate osteoclast function (Fig. 21-3). The story begins with RANK, which stands for receptor activator for nuclear factor- $\kappa$ B (NF $\kappa$ B), from the ability of the receptor to activate the NF $\kappa$ B transcriptional pathway on cells that bear RANK receptors, such as macrophages (and thus, osteoclasts). RANK is activated by interaction with RANK ligand (a cell surface molecule synthesized and expressed by bone stromal cells and osteoblasts). Stromal cells and osteoblasts also secrete macrophage colony-stimulating factor (M-CSF) that attaches to a distinct macrophage cell surface receptor. M-CSF and RANKL conspire to convert macrophages into bone-crunching osteoclasts. RANK activation is therefore essential for osteoclast formation. The resorptive activity induced by the RANK-RANK ligand pathway is regulated by a molecule called osteoprotegerin (OPG), secreted by osteoblasts and stromal cells. OPG is a "decoy receptor" that can bind RANK ligand and thus prevent it from binding to RANK. Binding of RANK ligand to OPG instead of RANK curtails osteoclast formation and bone-resorbing activity. Dysregulation of RANK ligand, and OPG interactions is likely a major contributor in the pathogenesis of osteoporosis. Such dysregulation can be caused by various reasons, including aging, changes in cytokine environment, and estrogen deficiency (Fig. 21-4) and its effects. The final common pathway in osteoporosis involves an imbalance of osteoblast bone formation and osteoclast bone resorption.

**Age-related changes.** With increasing age, osteoblasts replicate and synthesize matrix with various growth factors deposited in the ECM also tend to become less potent with time. Unsurprisingly, as bone formation wanes with advancing age, osteoclasts retain their youthful vigor (Fig. 21-4). **Hormonal influences.** The decline in bone mass associated with menopause correlates with an annual decline of as much as 2% of cortical bone and 50% of trabecular bone within 30-40 years! It is estimated that 1 in 3 post-menopausal women will suffer an osteoporotic fracture (compared to 2-3% of men of the same age). **Effects are attributable in part to augmented cytokine production** (especially interleukin-1 and interleukin-6) which increases RANK-RANK ligand activity and diminishes OPG (see Fig. 21-4). Despite some compensatory mechanisms, the imbalance to keep pace with the osteoclast bone resorption. While estrogen replacement can ameliorate



increasingly associated with other cardiovascular risks (see [Chapter 10](#)). *Physical activity.* Bone remodeling, reduced physical activity increases bone loss. This effect is obvious in astronauts whose skeletal system has been "unloaded" in a gravity-free environment. Physical inactivity in older individuals also contributes to senile osteoporosis. Because the magnitude of skeletal loss is proportional to the number of load cycles, the type of physical activity is important. Thus, resistance training increases bone mass more effectively than endurance activities such as jogging. *Genetic factors.* Vitamin D deficiency accounts for approximately 75% of the maximal peak bone mass achieved in any given individual. A deficiency in calcium uptake, or PTH synthesis and responses. *Calcium nutritional state.* The majority of individuals have an insufficient dietary intake. Unfortunately, this calcium deficiency occurs during a period of rapid bone formation, and therefore they do not achieve the maximal peak bone that could be otherwise expected, and are therefore likely to develop osteoporosis at an earlier age. *Secondary causes of osteoporosis.* These include prolonged immobilization, which increases bone resorption and reduces bone synthesis.)





### Clinical Course

The clinical outcome of osteoporosis depends on which bones are involved. Thoracic and lumbar common, and produce loss of height and various deformities, including kyphoscoliosis that can co Pulmonary embolism and pneumonia are common complications of fractures of the femoral neck, 50,000 deaths annually.

Osteoporosis is difficult to diagnose because it remains asymptomatic until skeletal fragility is ann cannot be reliably detected in plain radiographs until 30%-40% of bone mass has already disappe phosphorus, and alkaline phosphatase are notoriously insensitive. The current state of the art for radiographic techniques to assess density, e.g., dual-energy absorptiometry and quantitative com

Osteoporosis prevention and treatment begins with adequate dietary calcium intake, vitamin D su regimen-starting before the age of 30-to increase the peak bone density. Calcium and vitamin D s reduce bone loss. Bisphosphonate administration is an important part of the therapeutic strategy i decrease bone resorption. Selective estrogen receptor agonists are another class of drugs that ac endogenous estrogens) but without the side effects associated with estrogen use. Parathyroid hor approach, and may be especially applicable for patients who cannot tolerate estrogen therapy.

### Paget Disease (Osteitis Deformans)

This unique skeletal disease is characterized by repetitive episodes of frenzied, regional osteocla (*osteolytic stage*), followed by exuberant bone formation (*mixed osteoclastic-osteoblastic stage*), i cellular activity (*osteosclerotic stage*). The net effect of this process is a *gain in bone mass*; howe and lacks strength.

Paget disease usually does not occur until mid-adulthood but becomes progressively more comm in prevalence in different populations; it is rare in the native populations of Scandinavia, China, Ja in whites in much of Europe, Australia, New Zealand, and the United States, affecting up to 10% c

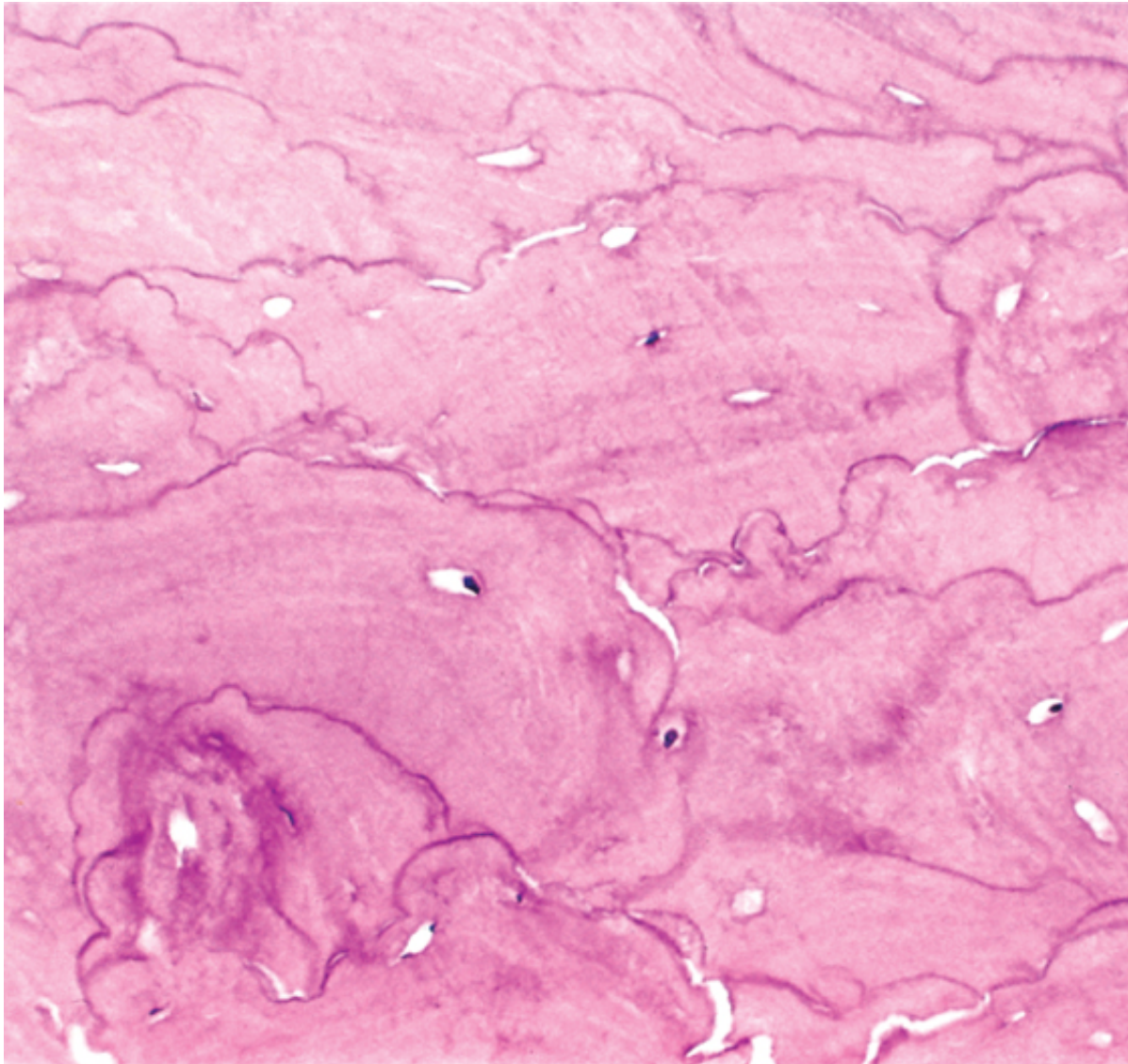
### Morphology

Paget disease may present as a solitary lesion (monostotic) or may occur at multip (polyostotic) with marked variation at each location. In the initial **lytic phase**, osteo associated Howship lacunae) are numerous and abnormally large. Osteoclasts per but the bone surfaces become lined by prominent osteoblasts. The marrow is repla tissue containing osteoprogenitor cells, as well as numerous blood vessels needec metabolic demands of the tissue. The newly formed bone may be woven or lamell; remodeled into a heightened caricature of lamellar bone. The pathognomonic histo **pattern** of lamellar bone (likened to a jigsaw puzzle) due to prominent cement line: units of lamellar bone (Fig. 21-5). As the osteoblastic activity burns out, the periost recedes and is replaced by normal marrow. Although thickened, the resulting corte deformation and fracture under stress.

### Pathogenesis

When he first described the disease, Sir James Paget attributed the skeletal changes to an inflam moniker *osteitis deformans*. Ironically, after many years and multiple alternative theories, he may suggests that a *paramyxovirus* infection ultimately underlies Paget disease. Paramyxovirus antigen paramyxovirus can be demonstrated in osteoclasts. The causal connection is that paramyxovirus cells, and this cytokine-as well as M-CSF-is produced in large amounts in pagetic bone. As noted osteoclasts. Nevertheless, as intriguing as these observations are, no infectious virus has been is pathogenic mechanisms are suggested by the observations that osteoclasts in Paget disease app activating agents such as vitamin D and RANK ligand

activating agents such as vitamin D and RANK ligand.



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Figure 21-5 Mosaic pattern of lamellar bone pathognomonic of Paget disease

### Clinical Course

The clinical findings depend on the extent and site of the disease. Paget disease is *monostotic* (involving one bone, usually the humerus) in about 15% of cases and *polyostotic* (pelvis, spine, and skull) in the remainder; the axilla is involved in as many as 80% of cases. Involvement of the ribs, fibula, and small bones of the hands and feet produce a plethora of skeletal, neuromuscular, and cardiovascular complications, most cases are incidental radiographic findings. Elevations in serum alkaline phosphatase and increased urinary calcium excretion reflect exuberant bone turnover.

In some patients, the early hypervascular bone lesions cause warmth of the overlying skin and swelling. In extensive polyostotic disease, hypervascularity can result in high-output congestive heart failure. Involvement of the skull, common symptoms, attributable to nerve impingement, include headache and deformities of the skull and impingement on cranial nerves. Back pain and may be associated with disabling fractures and nerve root compression. Affected long bones may be unable to appropriately remodel in response to the stress of weight-bearing. Brittle bones are prone to pathological fractures.

### **CRACKSTICK FRACTURES.**

The development of a sarcoma in association with osteoblastic lesions is a dreaded but fortunately occurring in only an estimated 1% of patients. The sarcomas are usually osteogenic, although their distribution generally parallels that of the Paget lesions, with the exception of vertebral bodies, where the prognosis of patients who develop secondary sarcomas is exceedingly poor, but in the absence of metastasis usually follows a relatively benign course. Most patients have mild symptoms that are readily controlled.

### **Rickets and Osteomalacia**

Both rickets and osteomalacia are manifestations of vitamin D deficiency or its abnormal metabolism. The fundamental change is defective bone mineralization resulting in overabundant nonmineralized osteoid where the mineral content of the remaining bone is normal, but the total bone mass is decreased. In children, which deranged bone growth produces distinctive skeletal deformities. *Osteomalacia* is the adult condition where the bone remodeling process is undermineralized, resulting in osteopenia and predisposition to fractures.

### **Hyperparathyroidism**

As discussed in [Chapter 20](#), parathyroid hormone (PTH) plays a central role in calcium homeostasis.

Osteoclast activation, increasing bone resorption and calcium mobilization. This effect is mediated by PTH production by osteoblasts. Increased resorption of calcium by the renal tubules. Increased synthesis of active vitamin D, 1,25-(OH)<sub>2</sub>-D, by the kidneys, which in turn enhances calcium mobilization from bone calcium by inducing RANKL.

The net result is an elevation in serum calcium, which, under normal circumstances, inhibits further PTH secretion. Inappropriate levels of PTH can result from autonomous parathyroid secretion (*primary hyperparathyroidism*) or underlying renal disease (*secondary hyperparathyroidism*; see also [Chapter 20](#)).

In either setting, *hyperparathyroidism leads to significant skeletal changes related to unabated osteoclastic activity*, although some sites can be more severely affected than others. PTH is directly responsible for the changes in *primary hyperparathyroidism*, but additional influences contribute to the development of bone disease in *secondary hyperparathyroidism*. In renal insufficiency there is inadequate 1,25-(OH)<sub>2</sub>-D synthesis that ultimately affects gastrointestinal absorption. The hyperphosphatemia of renal failure also suppresses renal  $\alpha_1$ -hydroxylase, further impairing vitamin D synthesis. Other factors include metabolic acidosis and aluminum deposition in bone.

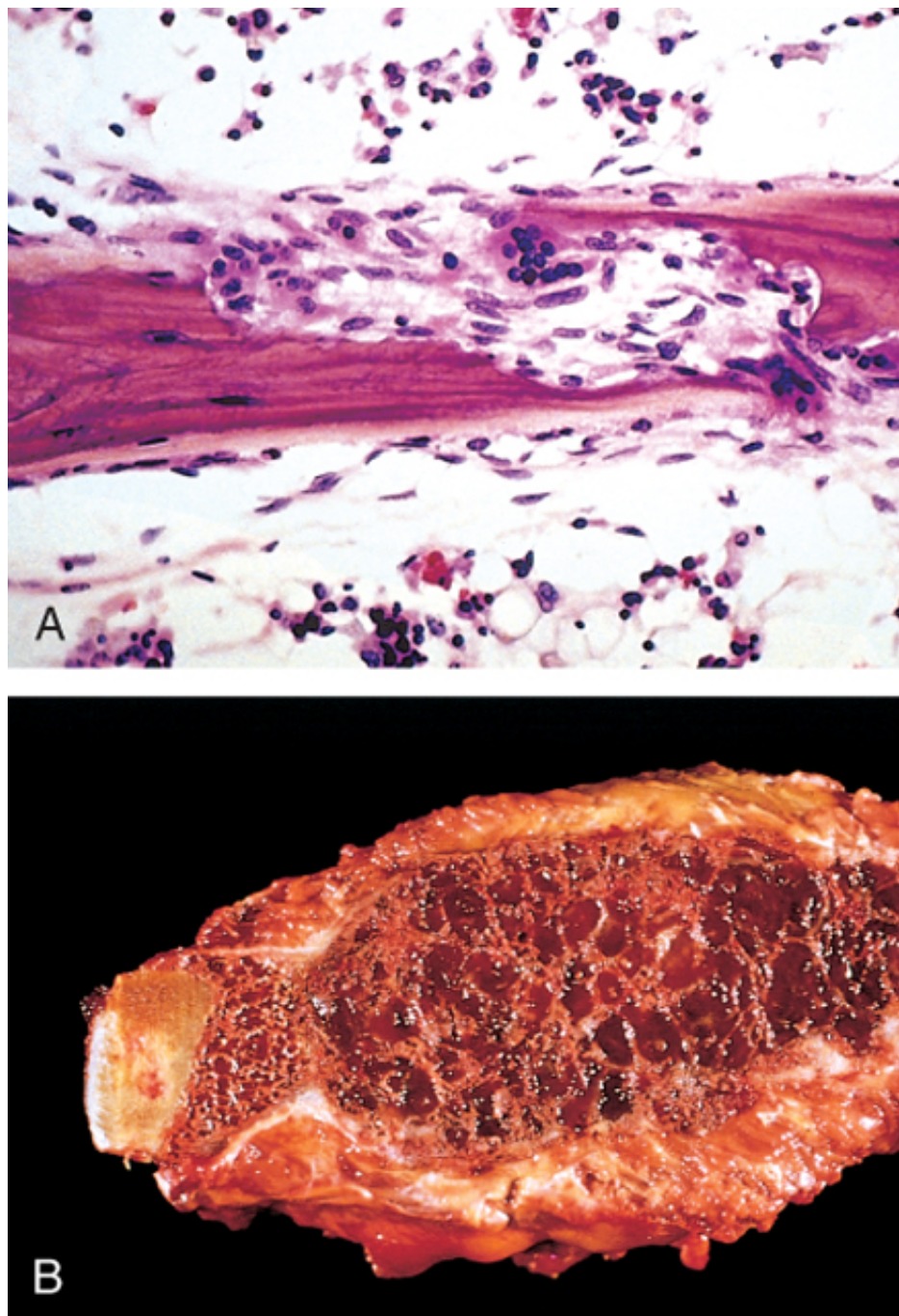
#### **Morphology**

The hallmark of PTH excess is **increased osteoclastic activity, with bone resorption**. Trabecular bone is lost and replaced by loose connective tissue. Bone resorption occurs in the subperiosteal regions and produces characteristic radiographic changes, best seen in the middle phalanges of the second and third fingers. Microscopically, excess activity is manifested by the presence of **increased numbers of osteoclasts and accompanying resorptive surfaces** ([Fig. 21-6A](#)). The marrow space contains increased amounts of loose fibrous tissue. Hemosiderin deposits are present, reflecting episodes of hemorrhage resulting from weakened bone. In some instances, collections of osteoclasts, reactive giant cells, form a distinct mass, termed a **brown tumor of hyperparathyroidism** ([Fig. 21-6B](#)). These are common in such lesions (hence the name **osteitis fibrosa cystica**), and they can be mistaken for bone neoplasms.

As bone mass decreases, affected patients are increasingly susceptible to fractures, bone deformities, and renal stones. Reduction of PTH level can result in complete lesion regression.







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 Figure 21-6 Bony manifestations of hyperparathyroidism. A, Osteoclasts gnawing into and disrupting lamellar bone ("brown tumor").

## SUMMARY

**Acquired Diseases of Bone Development** Nutritional deficiencies can affect altering the quality of the protein matrix (e.g., vitamin C is involved in collagen influencing bone mineralization (e.g., vitamin D is involved in calcium uptake from decreased bone mass and is clinically significant because it predisposes. Although osteoporosis is multifactorial, the two most common forms are *sen* aging-related losses of osteoblast function, and *postmenopausal osteoporosis* osteoclastic activity caused by the relative absence of estrogen. Paget disease



paramyxovirus infection and is caused by aberrant and excessive osteoclast exuberant-but structurally unsound-osteoblast deposition of bone. Primary or failure) overproduction of PTH (*hyperparathyroidism*) results in increased osteoclast resorption, leading to fractures and deformities.



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## FRACTURES

Fractures rank among the most common bone pathologies. They are classified as:

*complete* or *incomplete* *closed* when the overlying tissue is intact, or *compound* when the fracture extends into the overlying skin *comminuted* when the bone is splintered *displaced*, when the fractured bone is not aligned

If the break occurs at the site of previous disease (e.g., a bone cyst, a malignant tumor, or a brown tumor associated with elevated PTH), the result is a *pathologic fracture*. A *stress fracture* develops slowly over time as a collection of micro-fractures associated with increased physical activity, especially with repetitive weight on bone (as in military boot camps).

In all cases, the repair of a fracture is a highly regulated process that involves overlapping stages:

The trauma of the bone fracture ruptures associated blood vessels; the resulting blood coagulum creates a fibrin mesh scaffold to recruit inflammatory cells, fibroblasts, and endothelium. Degranulated platelets and marauding inflammatory cells subsequently release a host of cytokines (e.g., platelet-derived growth factor and FGF) that activate bone progenitor cells, and within a week, the involved tissue is primed for new matrix synthesis. This *soft tissue callus* is able to hold the ends of the fractured bone in apposition, but it is non-calcified and cannot support weight bearing. Bone progenitors in the medullary cavity deposit new foci of woven bone, and activated mesenchymal cells at the fracture site differentiate into cartilage-synthesizing chondroblasts. In uncomplicated fractures, this early repair process peaks within 2-3 weeks. The newly formed cartilage acts as a nidus for *endochondral ossification*, recapitulating the process of bone formation in epiphyseal growth plates. This connects the trabeculae in adjacent bone. With ossification, the fractured ends are bridged by a *bony callus*. Although excess fibrous tissue, cartilage, and bone are produced in the early callus, subsequent weight-bearing leads to resorption of the callus from non-stressed sites; at the same time there is fortification of regions that support greater loads. This callus remodeling restores the original size and shape of the bone, including the spongy cancellous architecture of the medullary cavity.

The healing of a fracture can be disrupted by many factors:

Displaced and comminuted fractures frequently result in some deformity; devitalized fragments of splintered bone require resorption, which delays healing, enlarges the callus, and requires inordinately long periods of remodeling that may never completely normalize. Inadequate immobilization permits constant movement at the fracture site so that the normal constituents of callus do not form. In this case, the healing site is composed mainly of fibrous tissue and cartilage, perpetuating the instability and resulting in delayed union and nonunion. Too much motion along the fracture gap (as in nonunion), causes the central portion of the callus to undergo cystic degeneration; the luminal surface can actually become lined by synovial-like cells, creating a false joint, or *pseudoarthrosis*. In the setting of a nonunion or pseudoarthrosis, normal healing can only be achieved if the interposed soft tissues are removed and the fracture site stabilized. *Infection* (a risk in comminuted and open fractures) is a serious obstacle to fracture healing. The infection must be eradicated before successful bone reunion and remodeling can occur. Bone repair will obviously be impaired by inadequate levels of

calcium or phosphorus, vitamin deficiencies, systemic infection, diabetes, and vascular insufficiency.

Generally, with uncomplicated fractures in children and young adults, practically perfect reconstitution is the norm. In older age groups, or for fractures occurring with an underlying disease (e.g. osteoporosis), repair is frequently less than optimal and typically requires orthopedic intervention to achieve the best result.





## OSTEONECROSIS (AVASCULAR NECROSIS)

Ischemic necrosis with resultant bone infarction occurs relatively frequently. Mechanisms contributing to bone ischemia include:

vascular compression or disruption (e.g., following a fracture) steroid administration thromboembolic disease (e.g., nitrogen bubbles in caisson disease; see [Chapter 4](#)) primary vessel disease (e.g., vasculitis)

Most cases of bone necrosis are due to fracture or occur after corticosteroid use.

### Morphology

The pathologic features of bone necrosis are the same regardless of cause. Dead bone with empty lacunae is interspersed with areas of fat necrosis and insoluble calcium soaps. The cortex is usually not affected because of collateral blood supply; in subchondral infarcts, the overlying articular cartilage also remains viable because the synovial fluid can provide nutritive support. With time, osteoclasts can resorb many of the necrotic bony trabeculae; any dead bone fragments that remain act as scaffolds for new bone formation, a process called **creeping substitution**.

### Clinical Course

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Symptoms depend on the size and location of injury. *Subchondral infarcts* initially declare with pain during physical activity, becoming more persistent with time. *Medullary infarcts* are usually clinically silent except for large ones (e.g., with Gaucher disease, caisson disease, or sickle cell disease). Medullary infarcts are usually stable; subchondral infarcts, however, often collapse and can lead to severe osteoarthritis. Roughly 50,000 joint replacements are performed each year in the United States specifically to treat the consequences of osteonecrosis.



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## OSTEOMYELITIS

The term *osteomyelitis* formally designates inflammation of the bone and marrow cavity; as commonly used, however, it almost always implies infection. Osteomyelitis can be a complication of systemic infection but more frequently occurs as an isolated focus of disease; it can be an acute process or a chronic, debilitating illness. Although any microorganism can cause osteomyelitis, the most common etiologic agents are pyogenic bacteria and *Mycobacterium tuberculosis*.

### Pyogenic Osteomyelitis

Most cases of acute osteomyelitis are caused by bacteria. The offending organisms reach the bone by one of three routes: (1) hematogenous dissemination (most common); (2) extension from an infection in adjacent joint or soft tissue; or (3) traumatic implantation after compound fractures or orthopedic procedures. Overall, *Staphylococcus aureus* is the most frequent causal organism; its propensity to infect bone may be related to the expression of surface proteins that allow adhesion to bone matrix. *Escherichia coli* and group B streptococci are important causes of acute osteomyelitis in neonates, whereas *Salmonella* is an especially common pathogen in individuals with sickle cell disease. Mixed bacterial infections, including anaerobes, are typically responsible for osteomyelitis developing after bone trauma. In as many as 50% of cases, no organisms can be isolated.

### Morphology

The morphologic changes in osteomyelitis depend on the stage (acute, subacute, or chronic) and location of the infection. Causal bacteria proliferate, induce an acute inflammatory reaction, and cause cell death. Entrapped bone undergoes early necrosis; the dead bone in infected sites is called a **sequestrum**. Bacteria and inflammation can percolate throughout the Haversian systems to reach the periosteum. In children, the periosteum is loosely attached to the cortex; therefore, sizable **subperiosteal** abscesses can form and extend for long distances along the bone surface. Lifting of the periosteum further impairs the blood supply to the affected region, and both suppurative and ischemic injury can cause segmental bone necrosis. Rupture of the periosteum can lead to an abscess in the surrounding soft tissue and formation of a **draining sinus**. Sometimes the sequestrum crumbles and forms free foreign bodies that pass through the sinus tract.

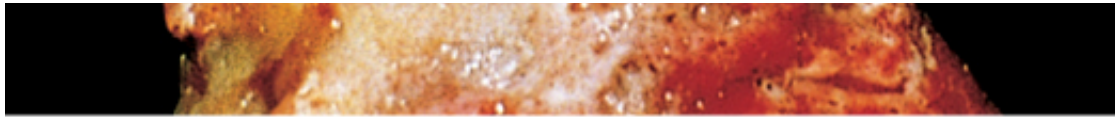
In infants (uncommonly in adults), epiphyseal infection can spread into the adjoining joint to produce suppurative arthritis, sometimes with extensive destruction of the articular cartilage and permanent disability. An analogous process can involve vertebrae, with an infection destroying intervertebral discs and spreading into adjacent vertebrae.

After the first week of infection chronic inflammatory cells become more numerous. Leukocyte cytokine release stimulates osteoclastic bone resorption, fibrous tissue ingrowth, and bone formation in the periphery. Reactive woven or lamellar bone can be deposited; when it forms a shell of living tissue around a segment of devitalized bone it is called an **involucrum** (Fig. 21-7). Viable organisms can persist in the sequestrum for years after the original infection.

### Clinical Features

Osteomyelitis classically manifests as an acute systemic illness with malaise, fever, leukocytosis, and throbbing pain over the affected region. Symptoms can also be subtle with only unexplained fever, particularly in infants, or only localized pain in the adult. Diagnosis is suggested by characteristic radiologic findings: a destructive lytic focus surrounded by a sclerotic rim. In many untreated cases, blood cultures are positive, but biopsy and bone cultures are usually required to identify the pathogen. A combination of antibiotics and surgical drainage is usually curative, but up to a quarter of cases do not resolve and persist as chronic infections. Chronicity may develop when there is delay in diagnosis, extensive bone necrosis, abbreviated antibiotic therapy, inadequate surgical debridement, and/or weakened host defenses. Besides occasional acute flare-ups, chronic osteomyelitis is also complicated by pathologic fracture, secondary amyloidosis, endocarditis, sepsis, development of squamous cell carcinoma in the sinus tract, and rarely osteosarcoma.





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 Figure 21-7 Resected femur from a person with chronic osteomyelitis. Necrotic bone (the sequestrum) visible in the center of a draining sinus tract is surrounded by a rim of new bone (the involucrum).

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### Tuberculous Osteomyelitis

Mycobacterial infection of bone has long been a problem in developing countries; with the resurgence of tuberculosis (due to immigration patterns and increasing numbers of immunocompromised hosts) it is becoming an important disease in other countries as well. Bone infection complicates an estimated 1% to 3% of cases of pulmonary tuberculosis. The organisms usually reach the bone through the bloodstream, although direct spread from a contiguous focus of infection (e.g., from mediastinal nodes to the vertebrae) can also occur. With hematogenous spread, *long bones and vertebrae are favored sites*. The lesions are often solitary but can be multicentric, particularly in patients with an underlying immunodeficiency. Because the tubercle bacillus is microaerophilic, the synovium, with its higher oxygen pressures, is a common site of initial infection. The infection then spreads to the adjacent epiphysis, where it causes a typical granulomatous inflammation with caseous necrosis and extensive bone destruction. *Tuberculosis of the vertebral bodies, or Pott disease, is an important form of osteomyelitis*. Infection at this site causes vertebral deformity and collapse, with secondary neurologic deficits. Extension of the infection to the adjacent soft tissues with the development of psoas muscle abscesses is fairly common in Pott disease.



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## BONE TUMORS

Primary bone tumors are considerably less common than are bone metastases from other primary tumors discussed at the end of this section.

*Primary bone tumors exhibit great morphologic diversity and clinical behaviors—from benign to aggressive—according to the normal cell of origin and apparent pattern of differentiation; Table 21-2 lists the six most common primary bone neoplasms, excluding multiple myeloma and other hematopoietic tumors. Overall, osteosarcoma is the most common, and among the benign tumors, osteochondroma and fibrous cortical defect occur most commonly. Osteosarcoma is the most common primary bone cancer, followed by chondrosarcoma and Ewing sarcoma. Benign tumors have counterparts, particularly before age 40; bone tumors in the elderly are much more likely to be malignant.*

**Table 21-2. Tumors of Bone**

<b>Tumor Type</b>	<b>Common Locations</b>	<b>Age (yr)</b>	<b>Morphology</b>
<b>Bone-Forming</b>			
<b>BENIGN</b>			
Osteoma	Facial bones, skull	40-50	Exophytic growths attached to bone surface; histologically benign
Osteoid osteoma	Metaphysis of femur and tibia	10-20	Cortical tumors, characterized by pain; histologically benign
Osteoblastoma	Vertebral column	10-20	Arise in vertebral transverse and spinous processes; histologically benign
<b>MALIGNANT</b>			
Primary osteosarcoma	Metaphysis of distal femur, proximal tibia, and humerus	10-20	Grow outward, lifting periosteum, and inward to form osteoid; cartilage may also be present
Secondary osteosarcoma	Femur, humerus, pelvis	>40	Complications of polyostotic Paget disease; histologically malignant
<b>Cartilaginous</b>			
<b>BENIGN</b>			
Osteochondroma	Metaphysis of long tubular bones	10-30	Bony excrescences with a cartilaginous cap; most common benign bone tumor
Chondroma	Small bones of hands and feet	30-50	Well-circumscribed single tumors resembling medullary cavity of bone; uncommonly multiple and hereditary
<b>MALIGNANT</b>			
Chondrosarcoma	Bones of shoulder, pelvis, proximal femur, and ribs	40-60	Arise within medullary cavity and erode cortex; cartilage-like or anaplastic
<b>Miscellaneous</b>			
Giant-cell tumor (usually benign)	Epiphysis of long bone	20-40	Lytic lesions that erode cortex; microscopically, round to spindle-shaped mononuclear cells; most common benign epiphyseal tumor
Ewing tumor (malignant)	Diaphysis and metaphysis	10-20	Arise in medullary cavity; microscopically, sheets of small round blue cells; aggressive neoplasm

Most bone tumors develop during the first several decades of life and have a propensity to originate in the metaphysis. Nevertheless, specific tumor types target certain age groups and anatomic sites; such clinical information is important for diagnosis. For instance, most osteosarcomas occur during adolescence, with half arising around the distal femur and half around the proximal tibia. In contrast, chondrosarcomas tend to develop during mid- to late adulthood and involve the epiphysis of long bones.

Most bone tumors arise without any prior known cause. Nevertheless, genetic syndromes (e.g., Li-Fraumeni syndrome) are associated with an increased risk of bone tumors.



...these tumors arise almost any prior trauma, cancer, osteomyelitis, genetic syndromes (e.g., ... syndromes; see [Chapter 6](#)) are associated with osteosarcomas, as are (rarely) bone infarcts, chronic radiation, and metal orthopedic devices.

In terms of clinical presentations, benign lesions are frequently asymptomatic and are detected as or a slowly growing mass. Occasionally, a sudden pathologic fracture is the first manifestation. Reevaluation of bone tumors; however, biopsy and histologic study are necessary for the final diagnosis.

### **Bone-Forming Tumors**

The tumor cells in the following neoplasms all produce bone that is usually woven and variably mineralized.

#### ***Osteoma***

*Osteomas* are benign lesions of bone that in many cases represent developmental aberrations or neoplasms. They are most commonly encountered in the head and neck, including the paranasal sinuses; they are typically seen in middle age. Osteomas are usually solitary and present as localized, slow-growing lesions on the bone surface. Multiple lesions are a feature of Gardner syndrome, a hereditary condition characterized by osteomas, epidermal cysts, and colorectal polyps. Although they may cause local mechanical problems (e.g., sinus cavity) and cosmetic deformities, they are not invasive and do not undergo malignant transformation.

#### ***Osteoid Osteoma and Osteoblastoma***

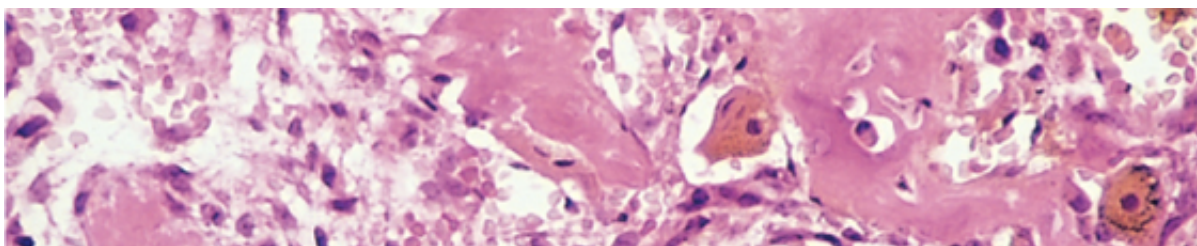
*Osteoid osteomas* and *osteoblastomas* are benign neoplasms with very similar histologic features, occurring in teenage years and 20s, with a male predilection (2 : 1 in osteoid osteomas). They are distinguished from each other by their radiographic appearance as well-circumscribed lesions, usually involving the cortex and medulla of the bone. The nidus of the tumor, termed the *nidus*, is characteristically radiolucent but may become mineralized over time. Osteoid osteomas most often in the proximal femur and tibia, and are by definition less than 2 cm, whereas osteoblastomas are larger, usually more than 2 cm. Pain is an almost universal complaint with osteoid osteomas, and is usually relieved by [aspirin](#). Osteoblastomas are more common in the spine; they also cause pain, although it is often more difficult to localize and is not responsive to aspirin. Incompletely resected lesions can recur. Malignant transformation is rare *unless* the lesion is associated with a preexisting malignancy.

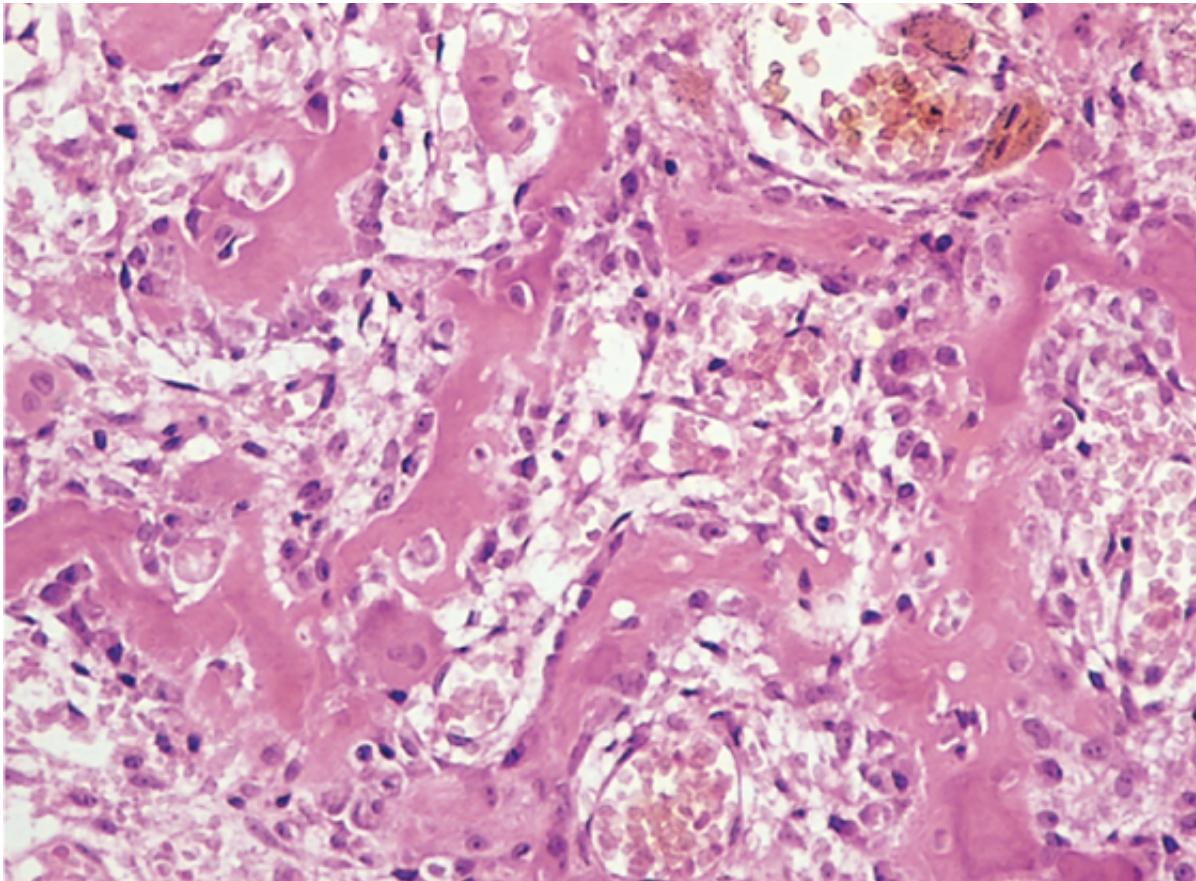
#### **Morphology**

Grossly, both lesions are round-to-oval masses of hemorrhagic gritty tan tissue. A nidus is often present at the edge of both types of tumors; however, it is much more conspicuous in osteoid osteomas. Microscopically, both neoplasms are composed of interlacing trabeculae of woven bone lined by osteoblasts ([Fig. 21-8](#)). The intervening stroma is loose, vascular connective tissue with occasional numbers of giant cells.

### **Osteosarcoma**

*Osteosarcoma is a bone-producing malignant mesenchymal tumor.* Outside of myeloma and lymphoma, it is the most common primary malignant tumor of bone, accounting for approximately 20% of primary bone cancers diagnosed annually in the United States. Osteosarcomas occur in all age groups but have two distinct peaks: one in adolescence and a second peak occurring in the elderly, usually with other conditions, including Paget disease, bone metastases, and prior radiation. Males are more commonly affected than women (1.6 : 1). Although any bone can be involved, most tumors occur in the long bones of the extremities, with almost 60% occurring about the knee, 15% around the hip, 10% around the shoulder, and 10% in the pelvis and spine. Several subtypes of osteosarcoma are recognized on the basis of the site of involvement within the bone, the degree of differentiation, solitary vs multicentric, presence of underlying disease, and histologic variants. The most common is primary, solitary, intramedullary, and poorly differentiated, producing a predominant osteoid matrix.





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 Figure 21-8 Osteoid osteoma showing randomly oriented trabeculae of woven bone rimmed by prominent osteovascular loose connective tissue.

### Morphology

Grossly, osteosarcomas are gritty, gray-white tumors, often exhibiting hemorrhage. Tumors frequently destroy the surrounding cortices and produce soft tissue masses spread extensively in the medullary canal, infiltrating and replacing the marrow, but penetrating the epiphyseal plate or entering the joint space. Tumor cells vary in size frequently have large hyperchromatic nuclei; bizarre tumor giant cells are common **production of mineralized or unmineralized bone (osteoid) by malignant cells diagnosis of osteosarcoma.** (Fig. 21-9B). The neoplastic bone is typically coarse and is deposited in broad sheets. Cartilage and fibrous tissue can also be present in a malignant cartilage is abundant, the tumor is called a **chondroblastic osteosarcoma**, as is spontaneous tumor necrosis.

### Pathogenesis

Several genetic mutations are closely associated with the development of osteosarcoma. In particular, 70% of sporadic tumors, and individuals with hereditary retinoblastomas (due to germ-line mutation) have a greater risk of developing osteosarcoma. Spontaneous osteosarcomas also frequently exhibit mutations in the cell cycle including *p53*, cyclins, cyclin-dependent kinases, and kinase inhibitors. Many osteosarcomas show growth.

### Clinical Features

Osteosarcomas typically present as painful enlarging masses, although a pathologic fracture can

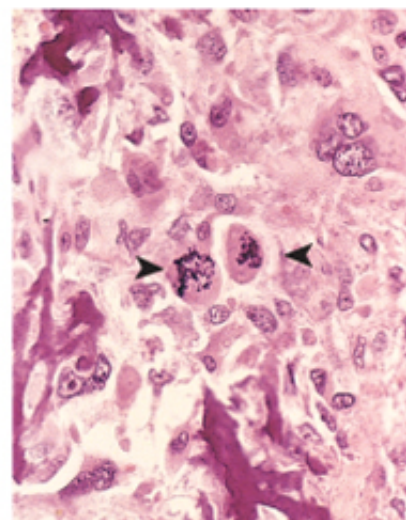
usually show a large, destructive, mixed lytic and blastic mass with indistinct infiltrating margins. The tumor lifts the periosteum, resulting in reactive periosteal bone formation. A triangular shadow of new bone formation (Codman triangle) is characteristic of osteosarcomas. Osteosarcomas typically spread early. At diagnosis, approximately 10% to 20% of patients have demonstrable pulmonary metastases.

Despite aggressive behavior, standard treatment with chemotherapy and limb-salvage therapy can result in survival rates up to 70%.

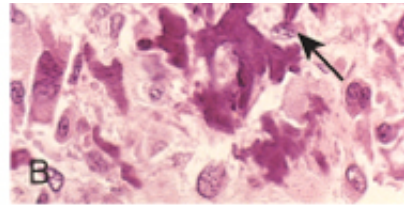
Secondary osteosarcomas occur in an older age group than do primary osteosarcomas. They may be associated with Paget disease or previous radiation exposure. Secondary osteosarcomas are highly aggressive tumors.

### **Cartilage-Forming Tumors**

These neoplasms produce hyaline or myxoid cartilage; fibrocartilage and elastic cartilage are rare. Chondrosarcomas, cartilaginous tumors, comprise a spectrum from benign, self-limited growths to highly aggressive malignant tumors. Benign cartilage tumors are much more common than malignant ones. Only the more common types are







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Figure 21-9 Osteosarcoma. **A**, Mass involving the upper end of the tibia. The tan-white tumor fills most of the metaphysis. It has infiltrated through the cortex, lifted the periosteum, and formed soft tissue masses on both sides of the bone. **B**, High magnification of the tumor showing a lacelike pattern of neoplastic bone (arrow) produced by anaplastic tumor cells. Note the wildly aberrant nuclei.

## Osteochondroma

Osteochondromas are also called *exostoses*; they are relatively common benign cartilage-capped projections from the underlying skeleton. Solitary osteochondromas are usually first diagnosed in late adolescence (male to female ratio of 3 : 1); multiple osteochondromas become apparent during childhood, occurring as *multiple hereditary exostosis*, an autosomal dominant disorder. Inactivation of both copies of the *EXT* gene in chondrocytes is implicated in both solitary and multiple osteochondromas. This tumor suppressor gene encodes glycosyltransferases essential for the synthesis of the proteoglycan component of cartilage. This finding and other molecular genetic studies support the concept that osteochondromas are developmental anomalies and not simple malformations.

Osteochondromas develop only in bones of endochondral origin arising at the metaphysis near the growth plate, especially about the knee; they tend to stop growing once the normal growth of the skeleton is complete. They can also develop from bones of the pelvis, scapula, and ribs, and in these sites are frequently sessile. Rarely, they can develop from bones of the hands and feet.

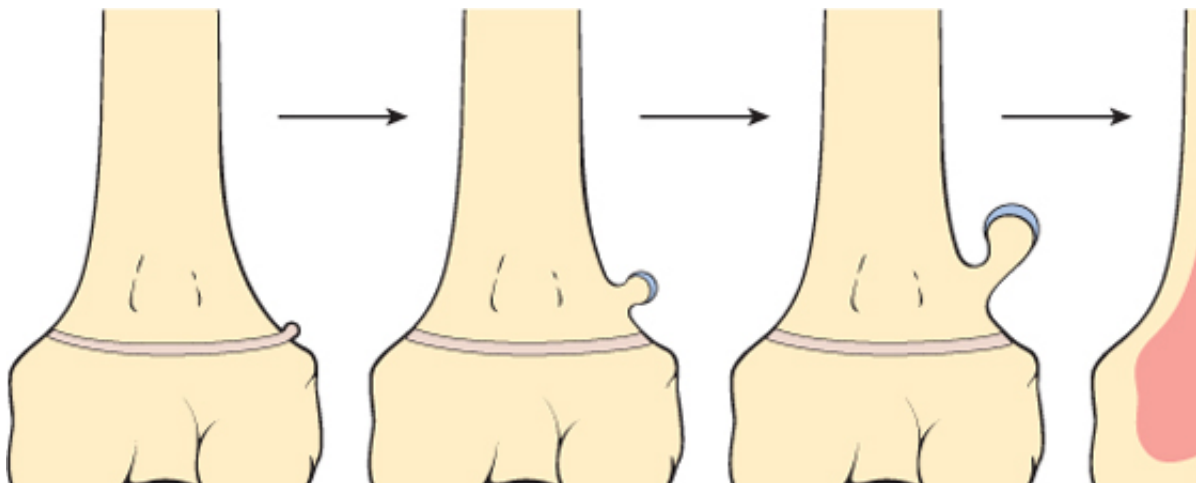
### Morphology

Osteochondromas vary from 1-20cm in size. The cap is benign hyaline cartilage, resembling the epiphyseal growth plate undergoing endochondral ossification. Newly formed bone forms the stalk of the tumor, and the stalk cortex merges with the cortex of the host bone.

### Clinical Features

Osteochondromas are slow-growing masses that are painful when they impinge on a nerve or if they rupture. They are often detected only incidentally. In multiple hereditary exostosis, deformity of the underlying bone is common due to abnormal epiphyseal growth. Osteochondromas rarely progress to chondrosarcoma or other sarcoma, although patients with multiple hereditary exostosis are at increased risk of malignant transformation.

## Chondroma





Chondromas are benign tumors of hyaline cartilage. When they arise within the medulla, they are called *enchondromas*. When they arise on the bone surface they are called *juxtacortical chondromas*. Enchondromas are usually diagnosed in patients who are typically solitary and located in the metaphyseal region of tubular bones, the favored sites being the distal radius and ulna of the forearm and the proximal tibia of the feet. *Ollier disease* is characterized by *multiple chondromas* preferentially involving one side of the body. *Maffucci syndrome* is characterized by *multiple chondromas associated with benign soft tissue angiomas*. Chondromas are composed of proliferating rests of growth plate cartilage.

### Morphology

Enchondromas are gray-blue, translucent nodules usually smaller than 3 cm. Microscopically, they consist of a well-circumscribed hyaline matrix and cytologically benign chondrocytes. At the periphery, there is peripheral ossification, while the center frequently calcifies and dies. In the hereditary multiple exostoses, islands of cartilage exhibit greater cellularity and atypia, making them difficult to distinguish from chondrosarcoma.

### Clinical Features

Most enchondromas are detected as incidental findings; occasionally they are painful or cause pathologic fracture. Small, unmineralized nodules of cartilage produce well-circumscribed oval lucencies surrounded by thin sclerotic margins. Calcified matrix exhibits irregular opacities. The growth potential of chondromas is limited, and most are cured if incompletely excised. Solitary chondromas rarely undergo malignant transformation, but those associated with hereditary multiple exostoses carry an increased risk. Maffucci syndrome is associated with an increased risk of developing other types of tumors, including carcinomas and brain gliomas.

### Chondrosarcoma

Chondrosarcomas comprise a variety of tumors sharing the ability to produce neoplastic cartilage (e.g., *intramedullary* vs *juxtacortical*), and histologic variants (see below). Chondrosarcomas occur most commonly in the long bones of the extremities; most patients are age 40 or older, with men affected twice as frequently as women.

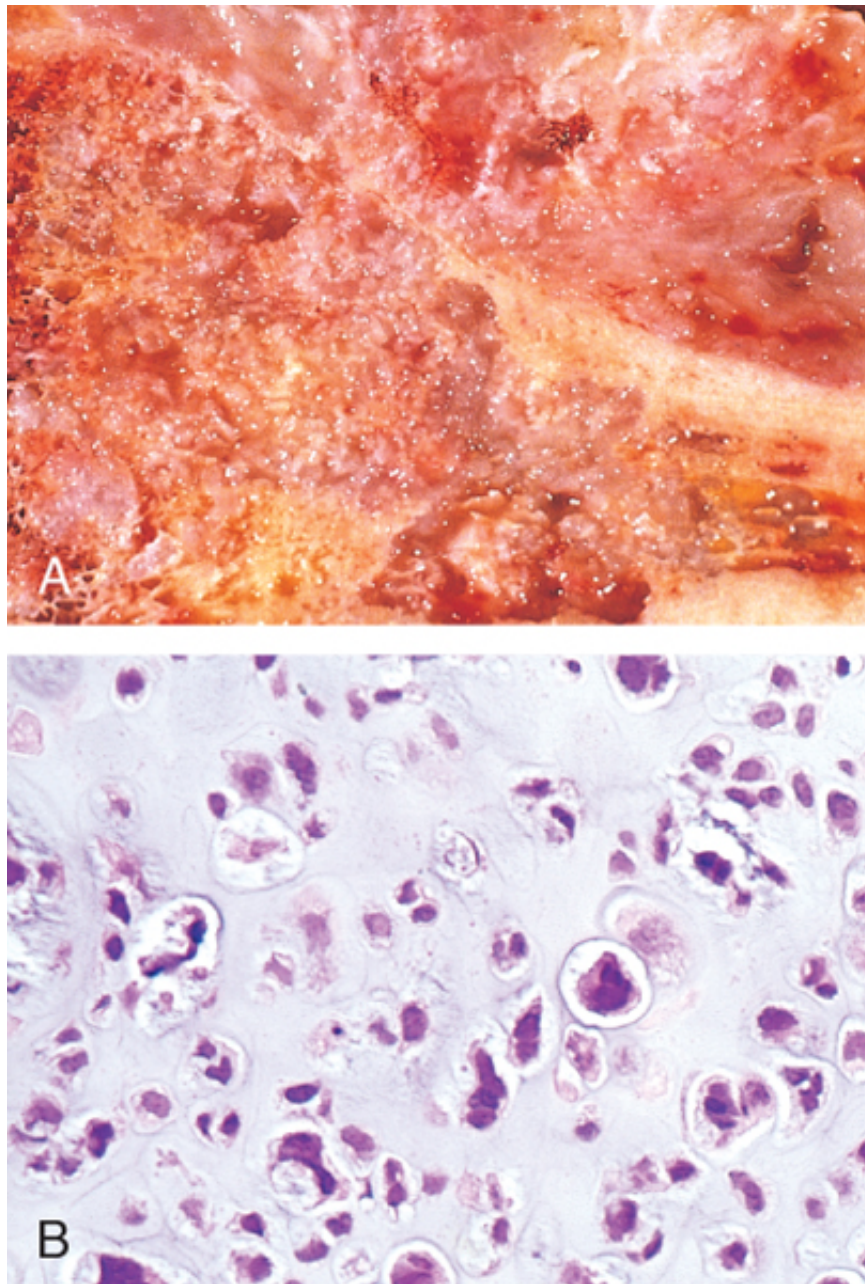
### Morphology

**Conventional chondrosarcomas** arise within the medullary cavity of the bone to form a soft, fleshy, glistening mass that often erodes the cortex (Fig. 21-11A).

They exhibit malignant hyaline and myxoid cartilage. In **myxoid chondrosarcoma**, the matrix is myxoid and gelatinous, and the matrix oozes from the cut surface. Spotty calcifications are common. Central necrosis can create cystic spaces. The adjacent cortex is thickened or eroded with broad pushing fronts into marrow spaces and the surrounding soft tissue. Tumors show increased cellularity, cytologic atypia, and mitotic activity (Fig. 21-11B). Low-grade tumors resemble hyaline cartilage. Higher grade lesions contain pleomorphic chondrocytes with frequent mitotic figures. Some lesions are present with lacunae containing two or more chondrocytes.

Approximately 10% of patients with conventional low-grade chondrosarcomas have a poorly differentiated component (**dedifferentiated chondrosarcomas**) that includes high-grade osteosarcomas. Other histologic variants include **clear-cell** and **mesenchymal chondrosarcomas**.





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 Figure 21-11 Chondrosarcoma. **A**, Islands of hyaline and myxoid cartilage expand the medullary cavity and grow mass. **B**, Anaplastic chondrocytes within a chondroid matrix.

### *Clinical Features*

Chondrosarcomas commonly arise in the pelvis, shoulder, and ribs; in contrast to enchondromas, distal extremities. They typically present as painful, progressively enlarging masses. A slowly growing thickening of the cortex, whereas a more aggressive high-grade neoplasm destroys the cortex and the more radiolucent the tumor the greater the likelihood that it is high grade. There is also a direct behavior of the tumor. Fortunately, most conventional chondrosarcomas are indolent and low-grade (90% vs 43% for grade 3 tumors); grade 1 tumors rarely metastasize, whereas 70% of the grade 2 tumors do. A prognostic feature, with tumors larger than 10 cm being significantly more aggressive than smaller tumors. Chondrosarcomas metastasize hematogenously, preferentially to the lungs and skeleton. Conventional chondrosarcomas are treated with surgery; chemotherapy is added for the mesenchymal and dedifferentiated variants because of their aggressive behavior.



## Fibrous and Fibro-Osseous Tumors

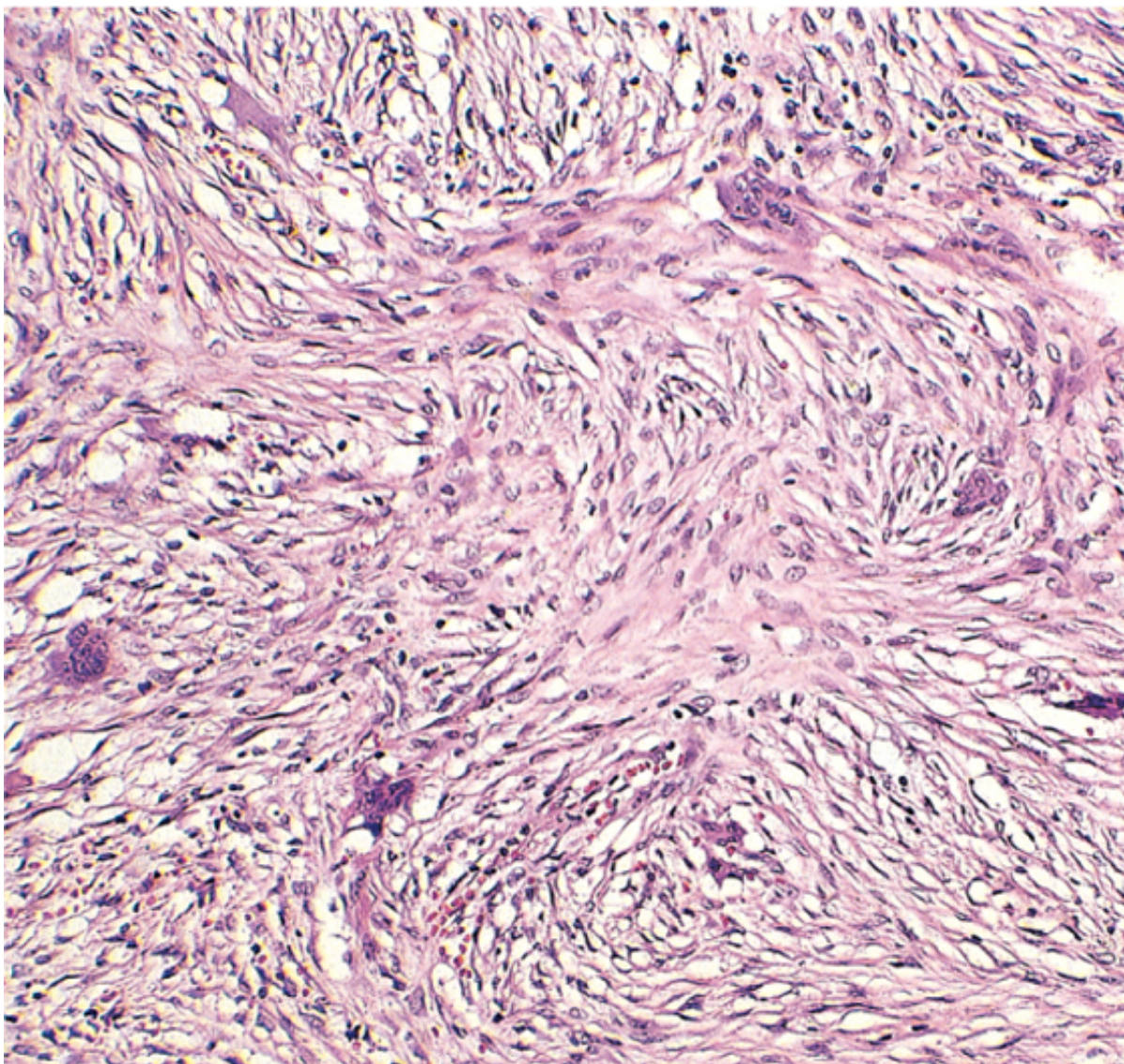
Fibrous tumors of the skeleton are extremely common and comprise a wide diversity of morphology.

### ***Fibrous Cortical Defect and Nonossifying Fibroma***

*Fibrous cortical defects* occur in 30% to 50% of all children older than age 2; they are probably developmental lesions rather than neoplasms. The vast majority are smaller than 0.5 cm and arise in the metaphysis of the distal femur, tibia, or humerus. They are usually unilateral but can be bilateral or multiple. Larger lesions (5-6 cm) develop into *nonossifying fibromas*.

#### **Morphology**

Fibrous cortical defects and nonossifying fibromas both present as sharply demarcated lesions surrounded by a thin zone of sclerosis. Grossly, they are gray to yellow-brown, and histologically they are cellular lesions composed of cytologically benign fibroblasts and activated macrophages. The fibroblasts classically exhibit a storiform (pinwheel) pattern.



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Figure 21-12 Fibrous cortical defect or nonossifying fibroma. Characteristic storiform pattern of spindle cells interspersed with multinucleated forms.



### **Clinical Features**

Fibrous cortical defects are asymptomatic and are usually only detected as incidental radiographic differentiation into normal cortical bone within a few years and do not require a biopsy. The few that present with pathologic fracture; in such cases biopsy is necessary to rule out other tumors.

### **Fibrous Dysplasia**

Fibrous dysplasia is a benign tumor that is probably more appropriately labeled a localized developmental bone defect. If the bone is present, but they fail to differentiate into mature structures. Fibrous dysplasia occurs as (1) involvement of a single bone (monostotic); (2) involvement of multiple bones (polyostotic); and (3) McCune-Albright syndrome. In McCune-Albright syndrome, skin pigmentation and endocrine abnormalities, especially precocious puberty. In McCune-Albright syndrome, skeletal, skin, and endocrine lesions result from a somatic (not hereditary) embryonic mutation that activates adenyl cyclase with resultant cyclic adenosine monophosphate overproduction and cell proliferation.

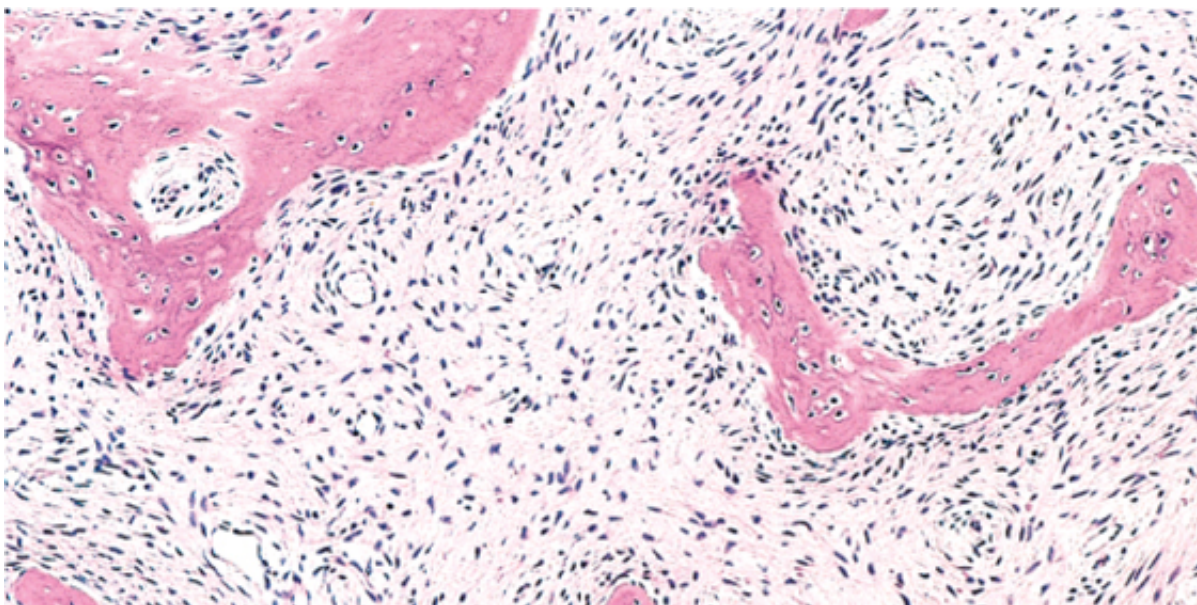
*Monostotic fibrous dysplasia* accounts for 70% of cases. It usually begins in early adolescence, and there is no gender predilection. In descending order of frequency, ribs, femur, tibia, jawbones, calvaria, are affected. Lesions are asymptomatic and usually discovered incidentally. However, fibrous dysplasia can cause distortion of bone, so that if the face or skull is involved, disfigurement can occur.

*Polyostotic fibrous dysplasia without endocrine dysfunction* accounts for the majority of the remainder. It usually begins in childhood and can progress into adulthood. In descending order of frequency, ribs, femur, tibia, jawbones, calvaria, are commonly involved. Craniofacial involvement is present in 50% of patients with moderate skeletal disease. Polyostotic disease tends to involve the shoulder and pelvic girdle and can cause spontaneous fractures.

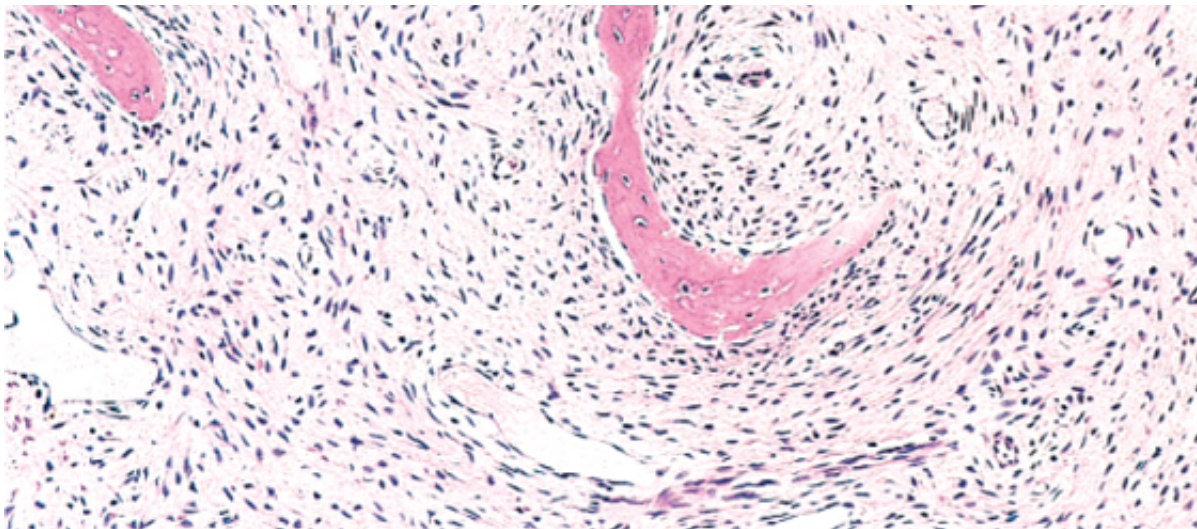
*McCune-Albright syndrome* accounts for 3% of all cases. The associated endocrinopathies include precocious puberty (in girls), hyperthyroidism, growth hormone-secreting pituitary adenomas, and primary adrenal hyperaldosteronism. The bone lesions are usually limited to the same side of the body. The cutaneous macules are classically large, dark, and café-au-lait in color.

### **Morphology**

Grossly, fibrous dysplasia is characterized by well-circumscribed, intramedullary lesions. The large masses expand and distort the bone. Lesional tissue is tan-white and gritty; radiographically, it shows the characteristic curved trabeculae of woven bone (mimicking Chinese characters), without osteoblastic rimming. Microscopically, the lesion is surrounded by a moderately cellular fibroblastic proliferation (Fig. 21-13).







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 Figure 21-13 Fibrous dysplasia. Curved trabeculae of woven bone arising in a fibrous tissue. Note the abs

#### *Clinical Course*

The natural history depends on the extent of skeletal involvement; individuals with monostotic disease. On x-ray, lesions exhibit a characteristic ground-glass appearance with well-defined margins. Symptomatic cases may require conservative surgery. Polyostotic involvement is frequently associated with progressive disease, and can lead to complications (e.g., fractures, long bone deformities, and craniofacial distortion). Rarely, polyostotic disease can occur following radiotherapy.

#### **Miscellaneous Bone Tumors**

##### ***Ewing Sarcoma and Primitive Neuroectodermal Tumor***

Ewing sarcoma and primitive neuroectodermal tumors (PNETs) are primary malignant small round cell tumors. Because they share an identical chromosome translocation, they should be viewed as the same tumor with different differentiation. PNETs demonstrate neural differentiation whereas Ewing sarcomas are undifferentiated.

These two malignancies account for 6% to 10% of primary malignant bone tumors. After osteosarcoma, they are the most common pediatric bone sarcomas. Most patients are 10 to 15 years old, and 80% are younger than 10 years. Males are affected more frequently than girls, and there is a striking racial predilection; blacks are rarely afflicted. The common chromosomal translocation that causes fusion of the *EWS* gene on 22q12 with a member of the *ETS* family of transcription factors. Fusion partners are the *FL1* gene on 11q24, and the *ERG* gene on 21q22. The resulting chimeric gene produces a transcription factor to stimulate cell proliferation. At a practical level, these translocations are of diagnostic value. 95% of patients with Ewing tumor have t(11;22) (q24;q12) or t(21;22) (q22;q12).

#### **Morphology**

Ewing sarcoma and PNETs arise in the medullary cavity and invade the cortex and soft tissue mass. The tumor is tan-white, frequently with hemorrhage and necrosis. Microscopically, it consists of uniform small, round cells that are slightly larger than lymphocytes with few mitoses and scant stroma (Fig. 21-14). The cells have scant glycogen-rich cytoplasm. The presence of rosettes (tumor cells circled about a central fibrillary space) indicates neural differentiation.

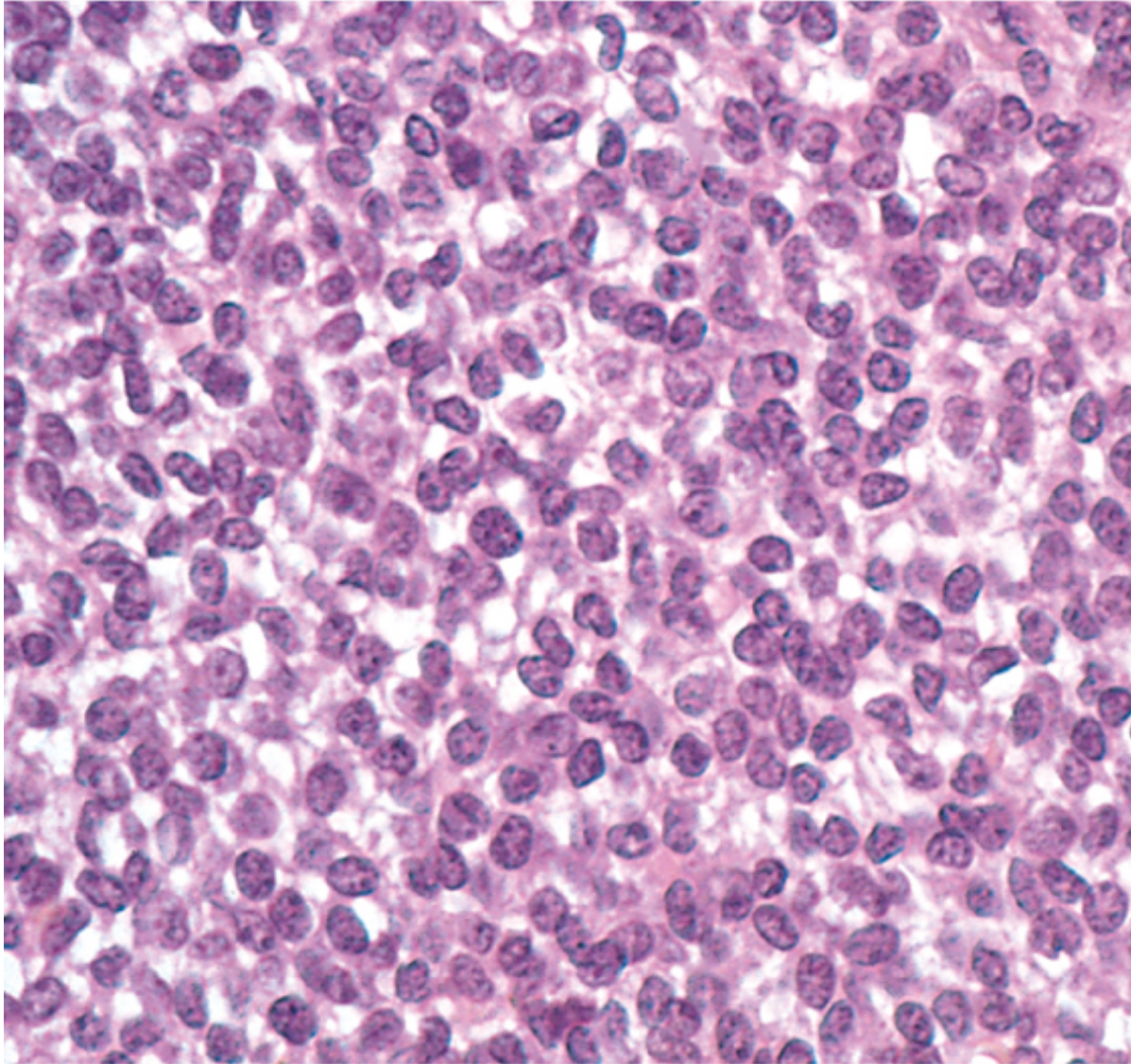
#### *Clinical Features*

Ewing sarcoma and PNETs typically present as painful enlarging masses in the diaphyses of long bones, ribs, or the pelvic flat bones. Some patients have systemic signs and symptoms, including fever, elevated ESR, and leukocytosis that can mimic infection. X-rays show a destructive lytic tumor with infiltrative margins. There is a characteristic periosteal reaction depositing bone in an onion-skin fashion.

issues. There is a characteristic periosteal reaction depositing bone in an onion-skin fashion.

Treatment includes chemotherapy and surgical excision with or without radiation. The 5-year survival is long-term durable remissions.

### ***Giant-Cell Tumor of Bone***



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Figure 21-14 Ewing sarcoma. Sheets of small round cells with scant, cleared

Giant-cell tumors (GCTs) are dominated by multinucleated osteoclast-type giant cells, hence the name. They are uncommon; it is benign but locally aggressive, usually arising in individuals in their 20s to 40s. The cellular component is likely a reactive macrophage population and the mononuclear cells are neoplastic. There are no significant abnormalities.

#### **Morphology**

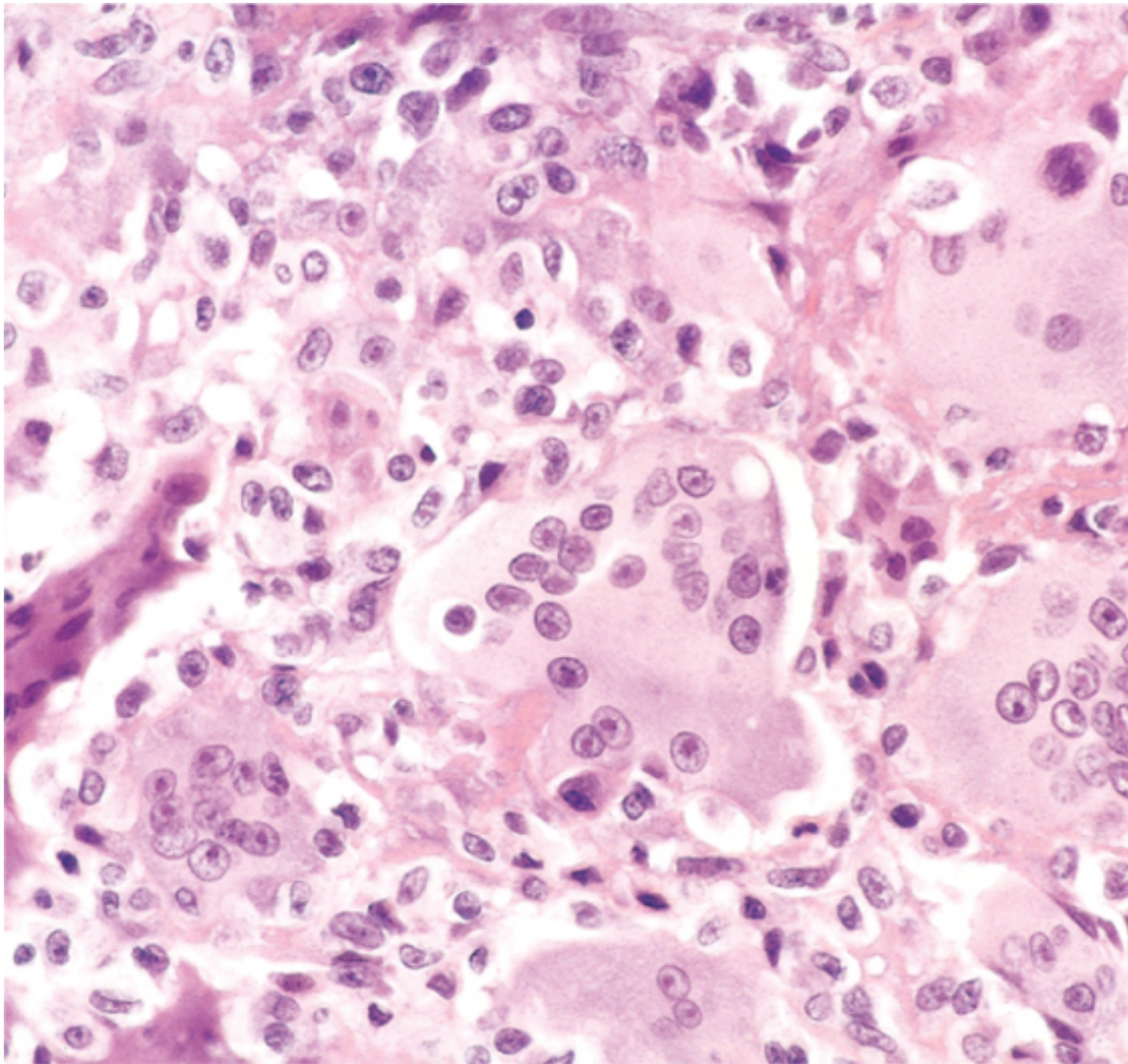
Tumors are large and red-brown with frequent cystic degeneration. They are composed of mononuclear cells with frequent mitoses, with scattered osteoclast-type giant cells and foamy nuclei (Fig. 21-15). Necrosis, hemorrhage, and reactive bone formation are also common.



### ***Clinical Course***

Although almost any bone can be involved, the majority of GCTs arise in the epiphysis of long bones (e.g., proximal tibia), frequently causing arthritis-like symptoms. Occasionally, GCTs present as pathologic fractures. Radiographically, GCTs are large, purely lytic, and eccentric; the overlying cortex is frequently deformed. Grossly, the tumor is a fleshy mass with a thin shell of reactive bone. Although GCTs are histologically benign, roughly half recur and 4% metastasize to the lungs.

### ***Metastatic Disease***



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Figure 21-15 Benign giant-cell tumor showing abundant multinucleated giant cells and a background of mononuclear stromal cells.

*Metastatic tumors are the most common malignant tumor of bone.* Pathways of spread include (1) hematogenous dissemination, and (3) intraspinal seeding. Any cancer can spread to bone, but certain cancers have a predilection. In adults more than 75% of skeletal metastases originate from cancers of the prostate and breast. In children, neuroblastoma, Wilms' tumor, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma are the common primary sources.

Most metastases involve the axial skeleton (vertebral column, pelvis, ribs, skull, sternum), proximal long bones, and the soft tissue of the extremities. Presumably, the red marrow in these areas, with its rich capillary network, slow blood flow, and

order. Presumably the red marrow in these areas, with its rich capillary network, slow blood flow, and cell implantation and growth.

The radiologic appearance of metastases can be purely lytic, purely blastic, or both. In lytic lesion metastatic cells secrete substances such as prostaglandins, interleukins, and PTHrP that stimulate cells themselves do not directly resorb bone. Similarly, metastases that elicit a sclerotic response stimulating osteoblastic bone formation. Most metastases induce a mixed lytic and blastic reaction

## SUMMARY

**Bone Tumors** Bone tumors of non-hematopoietic origin have diverse gross appearances, with clinical behaviors ranging from completely benign to rapidly progressive on a combination of clinical presentation (age, gender, and symptoms), site of occurrence, appearance, and histologic features. Most bone tumors are categorized according to the matrix they produce; chondroid and bony matrices are roughly equally represented. Metastatic tumors are the most common form of bone malignancy. Major tumor types can be subdivided into:

### Abnormal development

- Fibrous cortical defects-common developmental defects composed of benign fibroblasts
- Fibrous dysplasias-failure of normal bone elements to mature into mature structures
- Osteoma-developmental bony aberrations, typically at the skull base

### Benign neoplasms

- Osteoid osteoma-islands of woven bone, typically of the proximal femur or tibia
- Osteochondroma-cartilage-capped outgrowths at epiphyses

### Malignant neoplasms

- Osteosarcoma-malignant mesenchymal tumor forming bone; most common primary malignant bone tumor
- Chondrosarcoma-malignant mesenchymal tumor forming cartilage
- Ewing sarcoma-aggressive neural crest-derived neoplasm of adolescents

### Neoplasms of uncertain potential

- Giant cell tumor-occasionally (4%) malignant tumor composed of mononuclear cells and reactive osteoclast-like giant cells, typically at the epiphyses







## JOINTS

The joints are subject to a wide variety of disorders, including degeneration, infections, immune-mediated injury, metabolic derangements, and neoplasms. In this section we will confine our comments to some of the most common forms of arthritis, namely, degenerative joint disease (*osteoarthritis*), gout, and infectious arthritis, as well as the two most common benign joint tumors. Rheumatoid arthritis (RA), another important and potentially devastating joint disease, is discussed in detail in [Chapter 5](#).





## ARTHRITIS

### Osteoarthritis

Osteoarthritis, or *degenerative joint disease*, is the most common joint disorder. It is a frequent, if important cause of physical disability in individuals over the age of 65. *The fundamental feature of articular cartilage*; any structural changes in the underlying bone are secondary. Although the term disease, and inflammatory cells can be present, osteoarthritis is primarily a degenerative disorder

In most cases, osteoarthritis appears insidiously with age and without apparent initiating cause (*p*. disease is usually *oligoarticular* (i.e., affecting only a few joints). In the unusual circumstance (less strikes in youth, there is typically some predisposing condition, such as previous traumatic injury, systemic disease such as diabetes, ochronosis, hemochromatosis, or marked obesity. In these se *osteoarthritis* and often involves one or several predisposed joints. Gender has some influence; knees affected in women, whereas hips are more commonly affected in men. It is estimated that the economic burden in the United States is more than \$33 billion annually.

### Morphology

The earliest structural changes in osteoarthritis include enlargement, proliferation, and clustering of chondrocytes in the superficial part of the articular cartilage. This process is accompanied by a decrease in the water content of the matrix with decreasing concentration of the proteoglycans (the matrix conveys turgor and elasticity). Subsequently, vertical and horizontal **fibrillation** and **fracture** occur as the superficial layers of the cartilage are degraded (Fig. 21-16A). Gross examination reveals a soft granular articular cartilage surface. Eventually, full-thickness portions of the cartilage are lost and the subchondral bone plate is exposed. Friction smooths and burnishes the exposed bone, giving it the appearance of polished ivory (**bone eburnation**) (Fig. 21-16B). The underlying cartilage becomes sclerotic and thickened. Small fractures can dislodge pieces of cartilage and subchondral bone, forming loose bodies (**joint mice**). The fracture gaps allow synovial fluid to be forced into the gaps, forming regions to form fibrous walled cysts. Mushroom-shaped **osteophytes** (bony outgrowths) form at the margins of the articular surface. In severe disease, a fibrous synovial **pannus** covers the articular surface.

### Pathogenesis

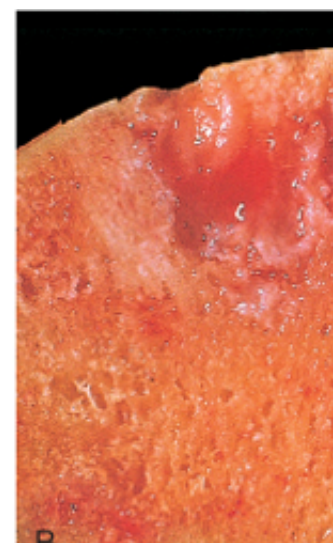
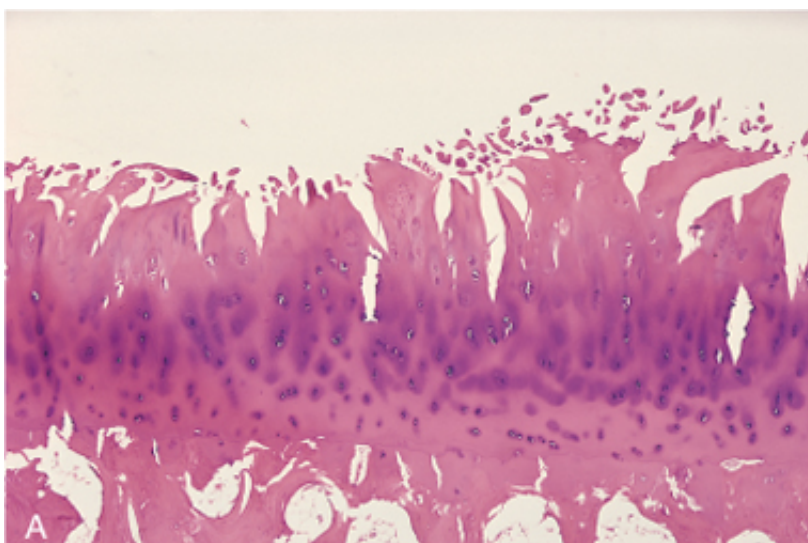


Figure 21-16 Osteoarthritis. **A**, Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B**, surface exposing subchondral bone. 2, Subchondral cyst. 3, Residual articl

*Articular cartilage bears the brunt of the degenerative changes in osteoarthritis.* Normal articular c with the synovial fluid, it provides virtually friction-free movement within the joint; and (2) in weight the joint surface in a manner that allows the underlying bones to absorb shock and weight. These elastic (i.e., to regain normal architecture after compression) and to have high tensile strength. Th proteoglycans and type II collagen, respectively, both produced by chondrocytes. As with adult bc undergoes matrix degradation and replacement. Normal chondrocyte function is critical to maintai any imbalance can lead to osteoarthritis.

Chondrocyte function can be affected by a variety of influences. Although osteoarthritis is not excl mechanical stresses and aging nevertheless figure prominently. *Genetic factors* also seem to con particularly in the hands and hips, but the responsible genes are not known. The risk of osteoarthri density, as well as sustained high estrogen levels.

Regardless of the inciting stimulus, early osteoarthritis is marked by degenerating cartilage contain The collagen network is also diminished, presumably as a result of decreased local synthesis and apoptosis is increased. Overall, cartilage tensile strength and resilience are compromised. In resp chondrocytes in the deeper layers proliferate and attempt to "repair" the damage by synthesizing i Although these reparative changes are initially able to keep pace, matrix changes and chondrocyt

#### Clinical Course

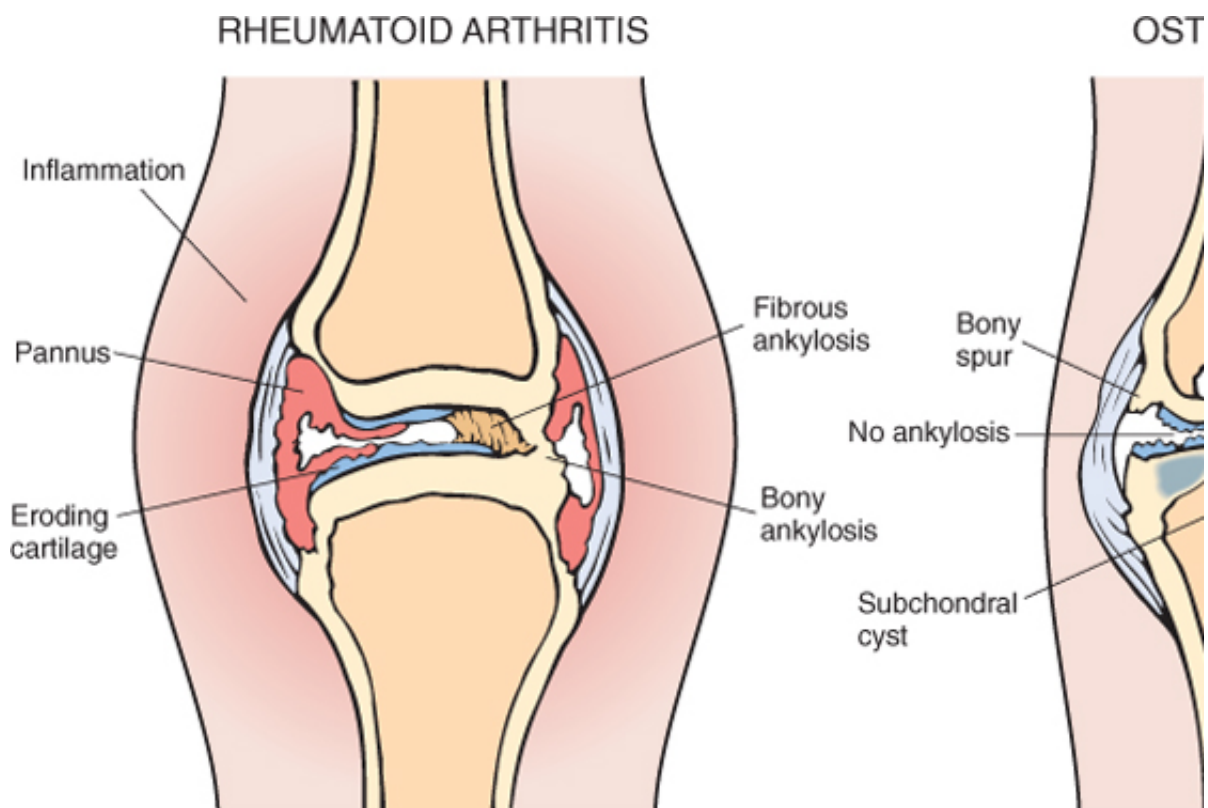


Figure 21-17 Comparison of the morphologic features of RA and osteoarthritis (also see Chapter 5 for

Osteoarthritis is an insidious disease, predominantly affecting patients beginning in their 50s and characterized by deep, aching pain exacerbated by use, morning stiffness, crepitus (grating or popping sensation in movement). Osteophyte impingement on spinal foramina can cause nerve root compression with resultant muscle atrophy, and neurologic deficits. Hips, knees, lower lumbar and cervical vertebrae, proximal and distal first carpometacarpal joints, and first tarsometatarsal joints of the feet are commonly involved. Healed, prominent osteophytes at the distal interphalangeal joints, are characteristic in women. Aside from the way to prevent or halt the progression of primary osteoarthritis; it can stabilize for years but is generally a significant joint deformity can occur, but unlike rheumatoid arthritis (Chapter 5), fusion does not take place. The morphologic features of these two disorders is shown in Figure 21-17.

## Gout

Gout is a disorder caused by the tissue accumulation of excessive amounts of *uric acid*, an end product of purine metabolism, by recurrent episodes of acute arthritis, sometimes accompanied by the formation of large crystalline deposits in joints. Joint deformity. All of these result from precipitation of monosodium urate crystals from supersaturated solution. The level of uric acid is an essential component of gout, not all such individuals develop gout, indicating that other factors contribute to the pathogenesis. Gout is traditionally divided into primary and secondary forms, according to whether or not there is an inborn metabolic defect that causes hyperuricemia. In *secondary gout* the cause of the hyperuricemia is the main or even dominant clinical disorder.

**Table 21-3. Classification of Gout**

Clinical Category	Metabolic Defect
<b>Primary Gout (90% of cases)</b>	
Enzyme defects unknown (85% to 90% of primary gout)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects-e.g., partial HGPRT deficiency (rare)	Overproduction of uric acid
<b>Secondary Gout (10% of cases)</b>	
Associated with increased nucleic acid turnover-e.g., leukemias Chronic renal disease Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretion Reduced renal excretion Overproduction of uric acid with increased urinary excretion (Lesch-Nyhan syndrome)

HGPRT, hypoxanthine guanine phosphoribosyl transferase.

## Morphology

The major morphologic manifestations of gout are acute arthritis, chronic tophaceous arthritis, and gouty nephropathy.

**Acute arthritis** is characterized by a dense neutrophilic infiltrate permeating the synovium. Long, slender, needle-shaped **monosodium urate crystals** are frequently found in the synovium as well as in small clusters in the synovium. The synovium is edematous and contains scattered mononuclear inflammatory cells. When the episode of crystallization ends, the crystals resolubilize, the attack remits.

**Chronic tophaceous arthritis** evolves from repetitive precipitation of urate crystals. The urates can heavily encrust the articular surfaces and form visible deposits in the joints. The synovium becomes hyperplastic, fibrotic, and thickened by inflammatory cells, and destroys the underlying cartilage, and leading to juxta-articular bone erosions. In severe cases, bony ankylosis ensues, resulting in loss of joint function.

**Tophi are the pathognomonic hallmarks of gout.** They are formed by large accumulations of monosodium urate crystals in the joints.



...tophi are the pathognomonic hallmark of gout, they are formed by large clefts surrounded by an intense inflammatory reaction of lymphocytes, macrophages, and attempting to engulf the masses of crystals (Fig. 21-18B). Tophi can appear in the and in the periarticular ligaments, tendons, and soft tissues, including the ear lobes skin of the fingertips. Superficial tophi can lead to large ulcerations of the overlying

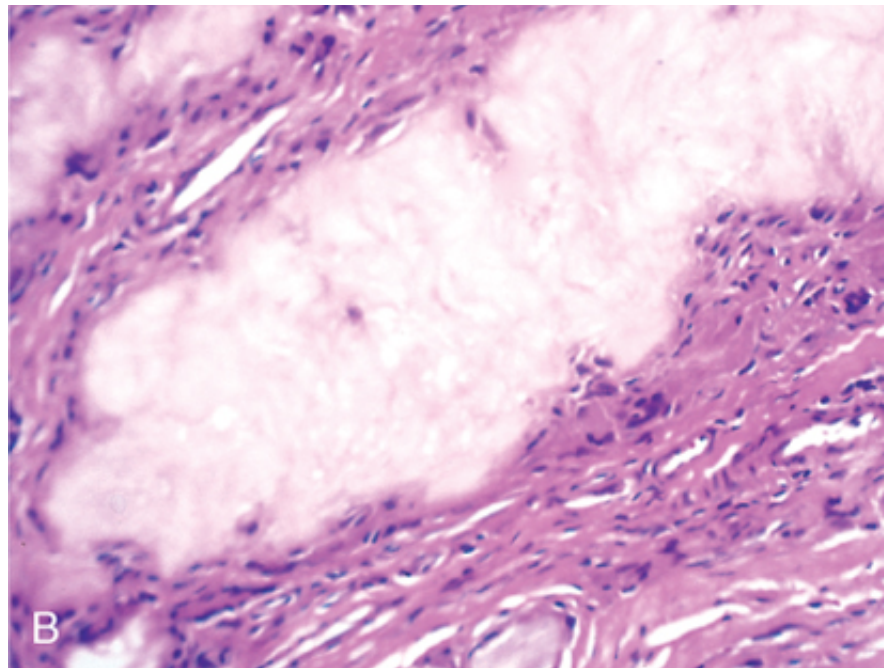
**Gouty nephropathy** refers to multiple different renal complications associated with variously forming medullary tophi, intratubular precipitations, or free uric acid crystals. Secondary complications such as pyelonephritis can occur, especially when there

### Pathogenesis

Elevated uric acid levels can result from overproduction of uric acid, reduced excretion, or both (secondary). It is characterized by a primary overproduction of uric acid. Less commonly, uric acid is produced at normal levels because of decreased renal excretion of urate. To understand these influences, a brief review of purine metabolism is warranted.

**Uric acid synthesis.** Uric acid is the end product of purine catabolism; consequently increased uric acid levels reflect an abnormality in purine nucleotide production. The synthesis of purine nucleotides involves two pathways: *de novo* and *salvage pathways* (Fig. 21-19). *The de novo pathway* is involved in the synthesis of purine precursors. The starting substrate is ribose-5-phosphate, which is ultimately converted into uric acid. Particularly important in the context of gout are (1) the negative feedback regulation of purine synthesis by uric acid (amido-PRT) and 5-phosphoribosyl-1-pyrophosphate (PRPP) synthetase by the purine nucleotides and (2) the activation of amido-PRT by its PRPP substrate. *The salvage pathway* is involved in the synthesis of purine bases, derived from dietary intake and by catabolizing nucleic acids and purine nucleotides. Purine nucleotides are formed in a single-step condensation between PRPP and hypoxanthine, guanine, or adenine, catalyzed by two transferases: hypoxanthine guanine phosphoribosyltransferase (HGPRT) and adenine phosphoribosyltransferase (APRT). **Uric acid excretion.** Circulating uric acid is freely filtered by the glomerulus and virtually all is reabsorbed in the proximal tubules of the kidney. A small fraction of the reabsorbed urate is subsequently secreted by the distal tubules into the urine.





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 Figure 21-18 Gout. **A**, Amputated great toe with white tophi involving the joint and soft tissues. **B**, Photomicrograph of urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells.

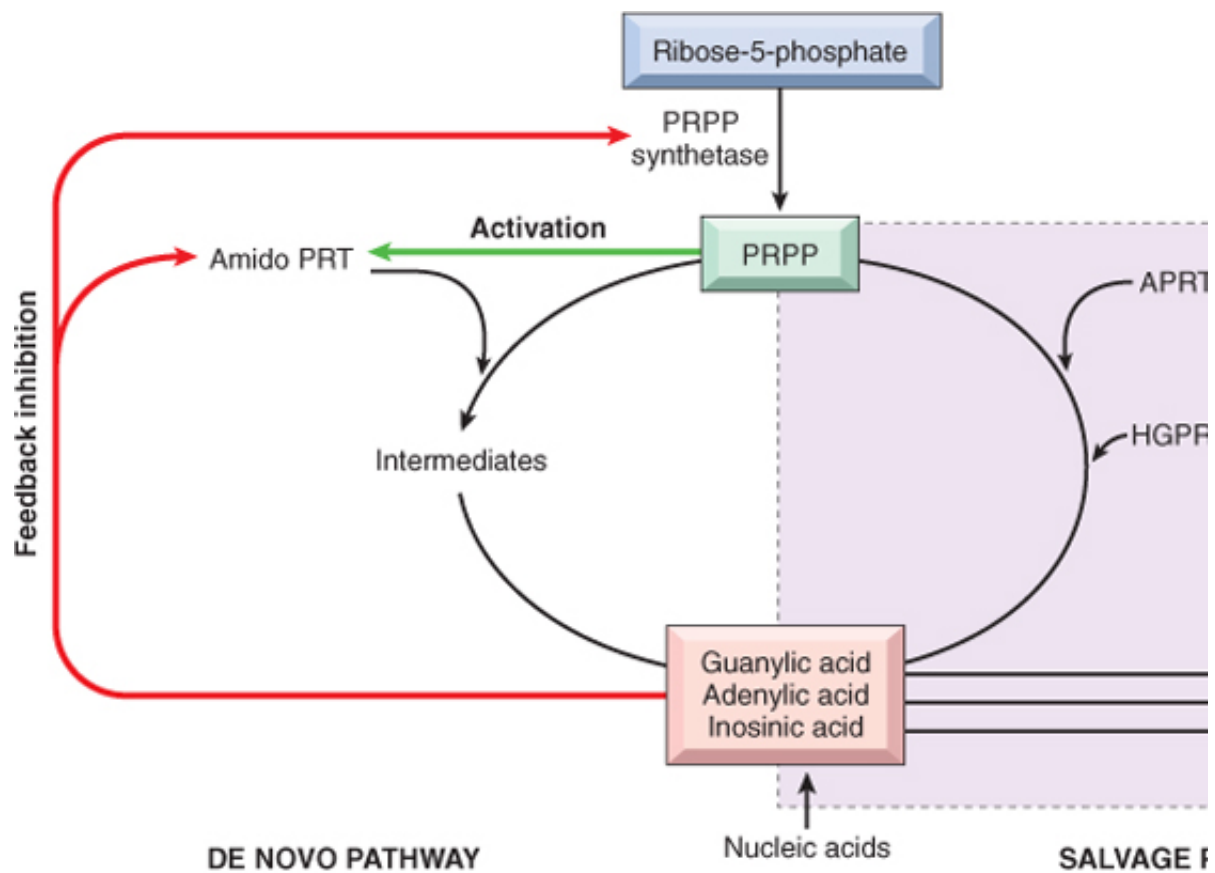


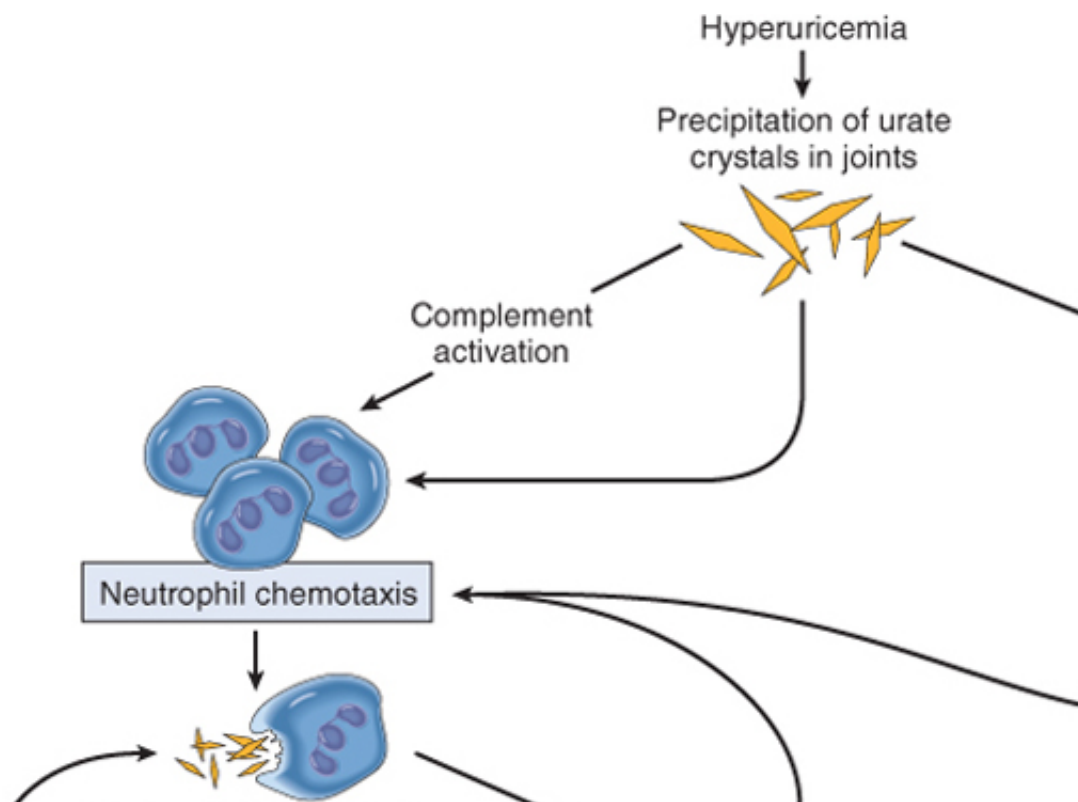
Figure 21-19 Purine metabolism. The conversion of PRPP to purine nucleotides is catalyzed by amido-PR I in the c salvage pathway. APRT, [adenosine](#)<sub>R</sub> phosphoribosyltransferase; HGPRT, hypoxanthine-guanine phospho pyrophosphate; PRT, phosphoribosyltransferase.

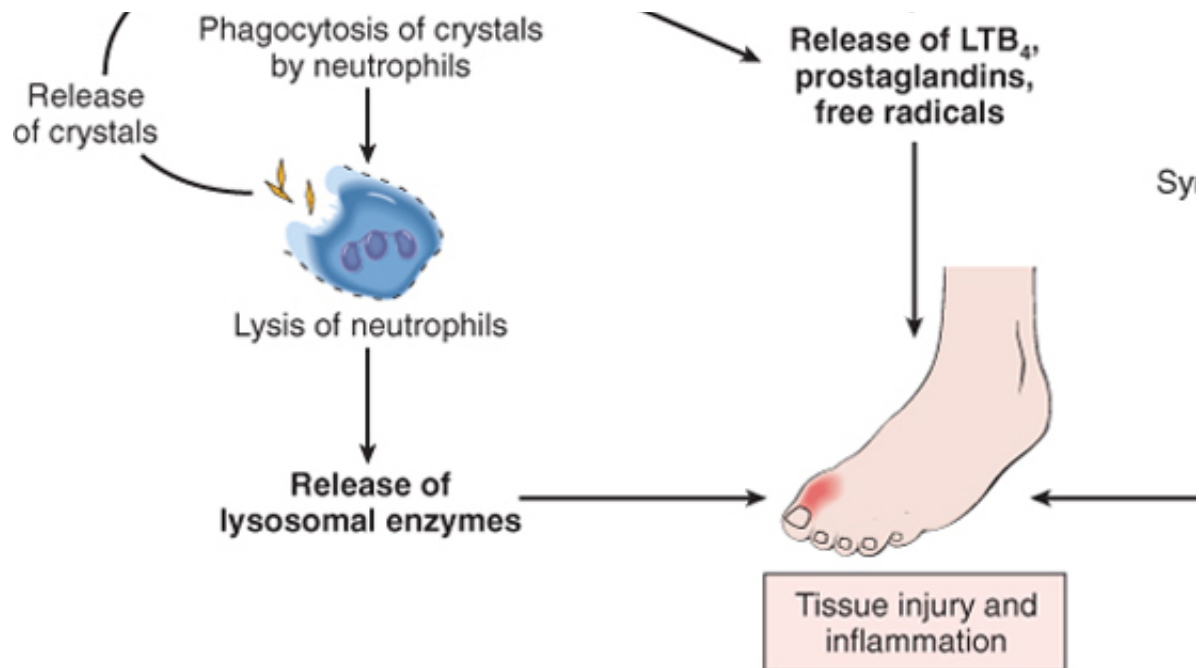
Although the cause of excessive uric acid biosynthesis in *primary gout* is unknown in most cases, defects. For example, complete lack of HGPRT gives rise to the *Lesch-Nyhan syndrome*. This X-l by excessive excretion of uric acid, severe neurologic disease with mental retardation, and self-m of gout!). Because of the almost complete absence of HGPRT, purine nucleotide synthesis via the two effects: an accumulation of PRPP, a key substrate for the de novo pathway, and increased ac PRPP and reduced feedback inhibition from purine nucleotides). As a consequence, de novo path resulting eventually in excess production of the uric acid end product. Less severe deficiencies of 3) cause clinically severe gouty arthritis, occasionally associated with mild neurologic disease.

In *secondary gout*, hyperuricemia can be caused by increased urate production (e.g., rapid cell ly: leukemia) or decreased excretion (chronic renal insufficiency), or both. Reduced renal excretion n thiazide diuretics, presumably because of effects on uric acid tubular transport.

Whatever the cause, increased levels of uric acid in the blood and other body fluids (e.g., synoviu monosodium urate crystals. This, in turn, triggers a chain of events that culminate in joint injury (F directly chemotactic, and can also activate complement to generate chemotactic C3a and C5a fra accumulation of neutrophils and macrophages in the joints and synovial membranes; in attemptin, become activated, leading to the release a host of additional mediators including chemokines, tox particularly leukotriene B<sub>4</sub>. The activated neutrophils also liberate destructive lysosomal enzymes by secreting a variety of proinflammatory mediators such as IL-1, IL-6, and TNF. While intensifying cytokines can also directly activate synovial cells and cartilage cells to release proteases (e.g., co resulting acute arthritis typically remits in days to weeks, even if untreated. Repeated bouts, howe seen in chronic tophaceous arthritis.

### Clinical Features





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Figure 21-20 Pathogenesis of acute gouty arthritis. IL, interleukin; LTB<sub>4</sub>, leukotriene B<sub>4</sub>; TN

Gout is more common in men than in women; it does not usually cause symptoms before the age described: (1) asymptomatic hyperuricemia, (2) acute gouty arthritis, (3) "intercritical" gout, and (4) *hyperuricemia* appears around puberty in males and after menopause in women. After a long interval the form of sudden onset of excruciating joint pain associated with localized erythema and warmth is uncommon, except possibly mild fever. The vast majority of first attacks are monarticular; 50% occur in the great toe, and 90% in the instep, ankle, heel, or wrist. Untreated, acute gouty arthritis may last for 1-2 weeks, completely resolves and the patient enters an *asymptomatic intercritical period*. Although some individuals experience a second episode within months to a few years. In the absence of appropriate therapy, attacks frequently become polyarticular. Eventually, after a decade or so, symptoms fail to resolve completely and the disease progresses to *chronic tophaceous gout*. At this stage, radiographs show characteristic juxta-articular deposits and loss of the joint space. Progression leads to severe crippling disease.

Renal manifestations of gout can appear as renal colic associated with the passage of gravel and gouty nephropathy. About 20% of individuals with chronic gout die of renal failure.

Numerous drugs are available to abort or prevent acute attacks of arthritis and mobilize tophaceous deposits because many aspects of gout are related to the duration and severity of hyperuricemia. Generally, treatment spans, but it can certainly impair quality of life.

### Pseudogout

*Pseudogout* is also known as *chondrocalcinosis* or more formally calcium pyrophosphate crystal disease. It first occurs in those age 50 or older, becoming more common with increasing age, and eventually in those age 85 or older. There is no gender or race predilection.

Although not all pathways that can lead to crystal formation are known, most probably they involve calcium pyrophosphate, resulting in its accumulation and eventual crystallization with calcium. In a hereditary transmembrane pyrophosphate transport channel, crystals develop relatively early in life and then

Much of the subsequent joint pathology in pseudogout involves the recruitment and activation of inflammatory cells (see above). Joint involvement can last from several days to weeks and may be monoarticular; the wrists, elbows, shoulders, and ankles, are most commonly affected. Ultimately, approximately 10% of patients develop joint damage. Therapy is supportive; no known treatment prevents or retards crystal formation.



joint damage. Therapy is supportive, no known treatment prevents or retards crystal formation.

### Infectious Arthritis

Microorganisms of any type can lodge in joints during hematogenous dissemination. Articular structures are inoculated or by contiguous spread from osteomyelitis or a soft tissue abscess. Infectious arthritis can lead to joint destruction and permanent deformities.

### Suppurative Arthritis

Bacteria can seed joints during episodes of bacteremia; joint infection with such microorganisms is called suppurative arthritis. Although virtually any bacteria can be causal, *Haemophilus influenzae* predominates in children, *Staphylococcus aureus* is the main causative agent in older children and adults, and *gonococcus* is prevalent during late adolescence. Individuals with sickle cell disease are prone to infection with *Salmonella* at any age. Both genders are affected by gonococcal arthritis, which occurs mainly in sexually active women. Those with deficiency of certain immune components are particularly susceptible to disseminated gonococcal infections and hence arthritis.

Classically, there is sudden onset of pain, redness, and swelling of the joint with restricted range of motion. An elevated erythrocyte sedimentation rate is common. In gonococcal infections, the course tends to be self-limiting. In nongonococcal suppurative arthritis, the infection involves only a single joint—usually the knee, hip, wrist, and sternoclavicular joints. Joint aspiration is typically purulent, and allows identification of the causative organism.

### Lyme Arthritis

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi*, transmitted by deer ticks. It is named for the Connecticut town where the disease was first recognized in the 1970s. With more than 300,000 cases annually, it is the leading arthropod-borne disease in the United States. As in another major spirochetal disease, syphilis, Lyme spirochetes involve multiple organ systems and is usually divided into three stages. In the early stage, at the site of the tick bite and cause an expanding area of redness, often with an indurated or pale center called "bull's-eye rash." In the *chronicum migrans*, may be accompanied by fever and lymphadenopathy but usually disappears. In the *disseminated stage*, spirochetes spread hematogenously and cause secondary annular skin lesions, muscle pain, cardiac arrhythmias, and meningitis, often with cranial nerve involvement. If the disease is not treated, it can be useful for serodiagnosis of *Borrelia* infection. Some spirochetes, however, escape host antibodies and persist in the central nervous system or as intracellular forms within endothelial cells. In the late stage, which occurs 2 or 3 years after the initial bite, Lyme *Borrelia* organisms cause a chronic arthritis, sometimes with associated neurologic and an encephalitis that varies from mild to debilitating.

*Lyme arthritis* develops in roughly 60% to 80% of untreated patients and is the dominant feature caused by immune responses against *Borrelia* antigens that cross-react with proteins in the joints. The pathogenesis of Lyme arthritis is not fully understood. The disease tends to be remitting and migratory, involving especially the knees, shoulders, elbows, and ankles, in descending order of frequency. Histologic findings with synovial hyperplasia, fibrin deposition, mononuclear cell infiltrates, and onion-skin thickening of the synovium. Morphology closely resembles rheumatoid arthritis. In only 25% of cases do silver stains reveal the organism. The diagnosis of Lyme arthritis may depend on the clinical story and/or appropriate serologic studies. Permanent joint damage and permanent deformities develop in roughly one of ten patients.

### SUMMARY

**Arthritis** *Osteoarthritis* (degenerative joint disease) is by far the most common type of arthritis. It represents a primary degenerative disorder of articular cartilage with matrix degradation and decreased synthesis. Inflammation is secondary. The vast majority of cases occur with no identifiable cause except increasing age. Local production of pro-inflammatory cytokines (interleukin-1, TNF, nitric oxide<sub>Rx</sub>), increased bone density, and sustained high estrogen levels are associated with osteoarthritis. *Gout and pseudogout*. Increased circulating levels of uric acid lead to uric acid crystal deposition in the joint space. *Pseudogout* is caused by calcium pyrophosphate (pseudogout) can lead to crystal deposition in the joint space. Inflammation and cell recruitment and activation leads to joint injury by degrading cartilage and causing fibrosis. Either direct infection of a joint space (*suppurative arthritis*) or cross-reactivity between immune responses to different antigens can cause infectious arthritis.

responses to systemic infections (e.g., in some cases of *Lyme arthritis*) can and injury.



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## JOINT TUMORS AND TUMOR-LIKE LESIONS

Primary neoplasms of joints are unusual; in general, they reflect the cells and tissue types (synovial cartilage) native to the joints. Benign tumors are much more frequent than their malignant counterparts; these structures are discussed below with the soft tissue tumors. In comparison, reactive *tumor-like cysts* are much more common than neoplasms; these typically result from trauma or degenerative

### Ganglion and Synovial Cysts

A *ganglion* is a small (<1.5 cm) cyst located near a joint capsule or tendon sheath; the wrist is an as firm to fluctuant pea-sized nodules. These are grossly translucent and microscopically lack a true cystic degeneration of connective tissue. Lesions can be multilocular through coalescence of adjacent fluid is similar to synovial fluid, although there is no communication with the joint space. Ganglions: Classically, these can be treated by "Bible therapy"; whacking them with a large tome is usually successful. Accumulation is uncommon.

Herniation of synovium through a joint capsule or massive enlargement of a bursa can produce a *Baker cyst* that occurs in the popliteal fossa.

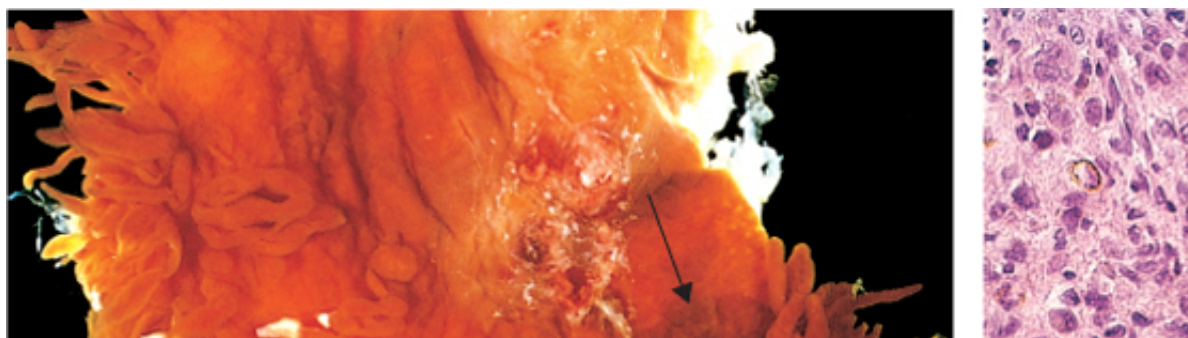
### Pigmented Villonodular Tenosynovitis and Giant-Cell Tumor of Tendon Sheath

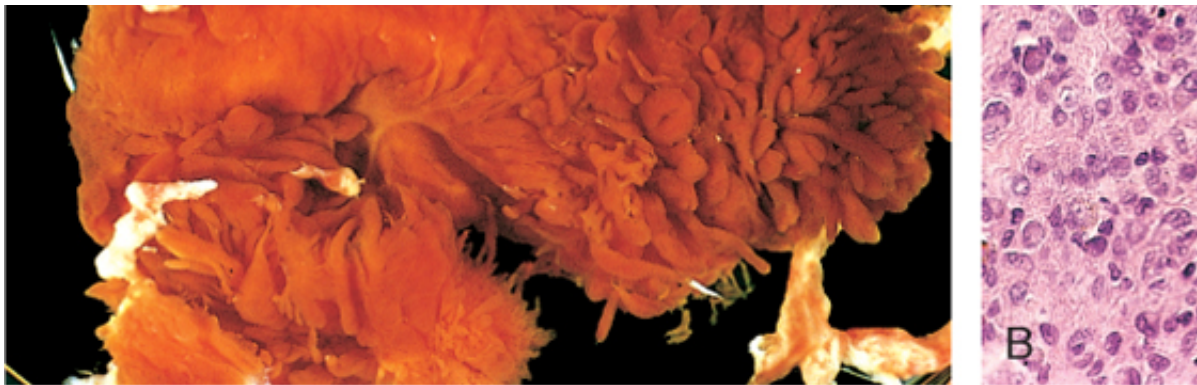
*Villonodular synovitis* is a catch-all term for several closely related benign neoplasms of synovium considered reactive proliferations (hence the designation *synovitis*), cytogenetic studies show that they are neoplastic, clonal proliferations. Classic examples include *pigmented villonodular synovitis* and *giant-cell tumor of tendon sheath* (GCT). Whereas PVNS tends to involve joints diffusely, GCT is a nodule. Both PVNS and GCT typically arise in people in their 20s to 40s without gender predilection.

#### Morphology

Grossly, PVNS and GCT are red-brown to orange-yellow. In PVNS the joint synovium is a mass of red-brown folds, finger-like projections, and nodules (Fig. 21-21A). In contrast, GCT is well-circumscribed and contained. Tumor cells in both lesions resemble synoviocytes (Fig. 21-21B). In PVNS the tumor cells spread along the surface and infiltrate the subsynovial compartment. In GCT the tumor cells form a dense aggregate. Other typical findings include hemosiderin deposits, foamy macrophages, and zones of scarring.

PVNS usually presents as a monoarticular arthritis; it affects the knee in 80% of cases, followed by the hip. The patient complains of pain, locking, and recurrent swelling. Tumor progression limits the range of movement into adjacent bones and soft tissues, causing confusion with other tumors. In contrast, GCT manifests as a painless mass frequently involving wrist and finger tendon sheaths; it is the most common soft tissue tumor of the hand. Involvement of adjacent bone occurs in approximately 15% of cases. Both lesions are amenable to surgical resection.





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 Figure 21-21 Pigmented villonodular synovitis (PVNS). **A**, Excised synovium with fronds and nodules typical of PVNS bulging the synovial lining.



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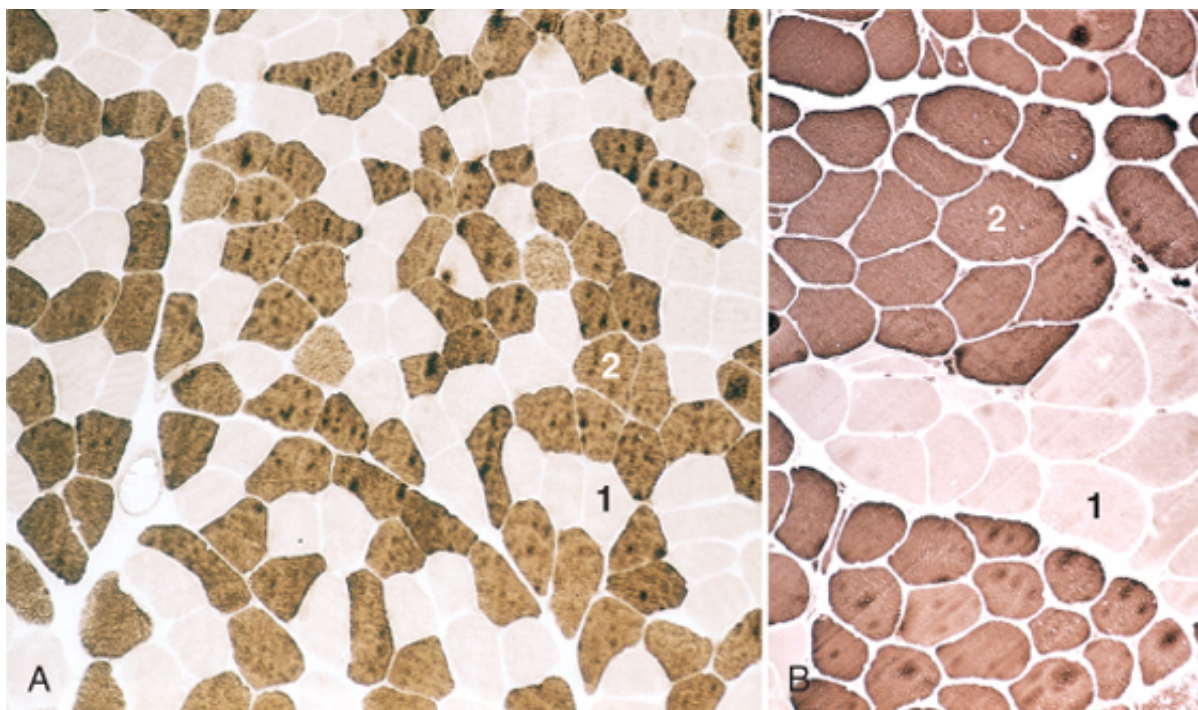




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## SKELETAL MUSCLE

Normal skeletal muscle development and function critically depend on a tight integration with the nervous system (Chapter 23). The principal element of this integrated system is called the *motor unit*. It is comprised of the spinal cord, its associated peripheral axon and distal neuromuscular junction, and finally, the skeletal muscle fibers. Depending on the nature of the nerve fiber doing the innervation, the associated skeletal muscle fibers are divided into two subpopulations; *type I "slow twitch"* or *type II "fast twitch"* fibers. The different fibers are distinguished by their biochemical attributes, and can be identified using specific staining techniques. A single "type I" or "type II" fiber is a single muscle fiber and these fibers are usually randomly scattered in a "checkerboard pattern" within a muscle (Fig. 21-22A). A helpful mnemonic for type I fibers is "one slow fat red ox" referring to type I fibers being dependent on *fat* catabolism for energy through mitochondrial oxidative phosphorylation; the *red* refers to the color of the fibers where fiber type grouping in different muscles (e.g., thigh vs. breast meat) is quite pronounced. Type II fibers ("two fast glycogen white anaerobes") is not nearly so memorable.



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Figure 21-22 **A**, ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of fiber types. **B**, in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C**, A cluster of fibers (arrow).

Diseases that affect skeletal muscle can involve any portion of the motor unit; these include primary abnormalities of the neuromuscular junction, and a wide variety of disorders primarily affecting the muscle. In the purposes of the following discussion, we will divide skeletal muscle disease into 1) disorders characterized by myofiber atrophy, 2) the more common muscular dystrophies, 3) selected congenital, toxic, and inflammatory myopathies such as *dermatomyositis* are discussed in Chapter 5), and 4) disorders of the neuromuscular junction. In this section we will also briefly touch on primary skeletal muscle tumors.





## MUSCLE ATROPHY

Muscle atrophy is a non-specific response in a variety of muscle disorders. It is characterized by abnormally small myofibers; the type of fibers affected by the atrophy, their distribution in the muscle, and their specific morphology help identify the etiology of the atrophic changes.

Clearly loss of muscle innervation causes atrophy of the associated fibers. As discussed in detail below, neurogenic atrophy is characterized by involvement of both fiber types and by clustering of myofibers into small groups. Simple disuse (e.g., prolonged bed rest, immobilization to allow healing of a bone fracture, etc.) can also cause profound atrophy. Exogenous glucocorticoids or endogenous hypercortisolism (e.g., in Cushing syndrome) are another cause of muscle atrophy, typically involving proximal muscle groups more than distal ones. Disuse- and steroid-induced atrophy primarily affects the type II fibers and causes a random distribution of the atrophic myofibers. Finally, atrophic myofibers are also found in myopathies. As discussed later, the finding of additional morphologic changes like myofiber degeneration and regeneration, chronic remodeling of the tissue or inflammatory infiltrates are features that suggest a myopathic etiology.

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### Neurogenic Atrophy

Deprived of their normal enervation, skeletal fibers undergo progressive atrophy. It is important to recall that loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scattered over the field. However, following re-enervation, adjacent intact neurons send out sprouts to engage the neuromuscular junction of the previously de-enervated fibers. Once the new connection is established these fibers assume the type of the innervating neuron. In this manner, whole groups of fibers can eventually fall under the influence of the same neuron, and become the same fiber type (*fiber type grouping*) (Fig. 21-22B). In that setting, if the relevant enervating neuron now becomes injured, rather large coalescent groups of fibers are cut off from the trophic stimulation and wither away (*grouped atrophy*, Fig. 21-22C), a hallmark of recurrent neurogenic atrophy.



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## MUSCULAR DYSTROPHY

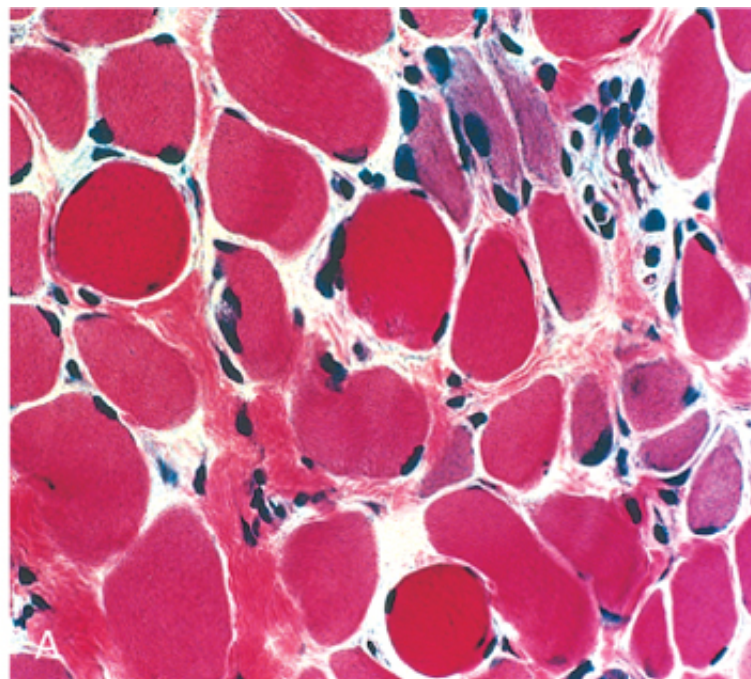
The muscular dystrophies are a heterogeneous group of inherited disorders, often presenting in childhood, characterized by progressive degeneration of muscle fibers leading to muscle weakness and, in advanced cases, muscle fibers are replaced by fibrofatty tissue. This histologic feature distinguishes myopathies (described later), which also present with muscle weakness.

### X-Linked Muscular Dystrophy (Duchenne and Becker Muscular Dystrophy)

The two most common forms of muscular dystrophy are X-linked: *Duchenne muscular dystrophy* (DMD) and *Becker muscular dystrophy* (BMD). DMD is the most severe and the most common form of muscular dystrophy, with an incidence of about 1 per 3500 live male births. DMD becomes clinically evident by age 5, with progression leading to wheelchair dependence by age 10 to 12 years, and death by the early 20s. Although both are involved in both BMD and DMD, BMD is less common and much less severe.

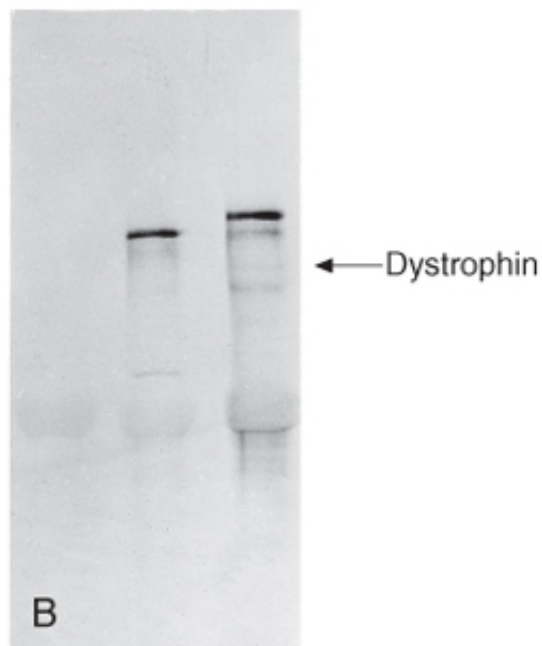
#### Morphology

The histologic features of DMD and BMD are similar and include **marked variation in fiber size**, caused by concomitant myofiber hypertrophy and atrophy. Many of the muscle fibers show a range of **degenerative changes**, including fiber splitting and necrosis, whereas other fibers show evidence of **regeneration**, including sarcoplasmic basophilic nuclear enlargement, and nucleolar prominence. **Connective tissue is increased** throughout the muscle (Fig. 21-23A). The definitive diagnosis is based on the demonstration of **absent staining for dystrophin** in immunohistochemical preparations or by western blot analysis of skeletal muscle. In the late stages of the disease, extensive fiber loss and adipose tissue infiltration are present in most muscle groups. Changes in cardiac muscle in either DMD or BMD include variable degrees of fiber hypertrophy and interstitial fibrosis.



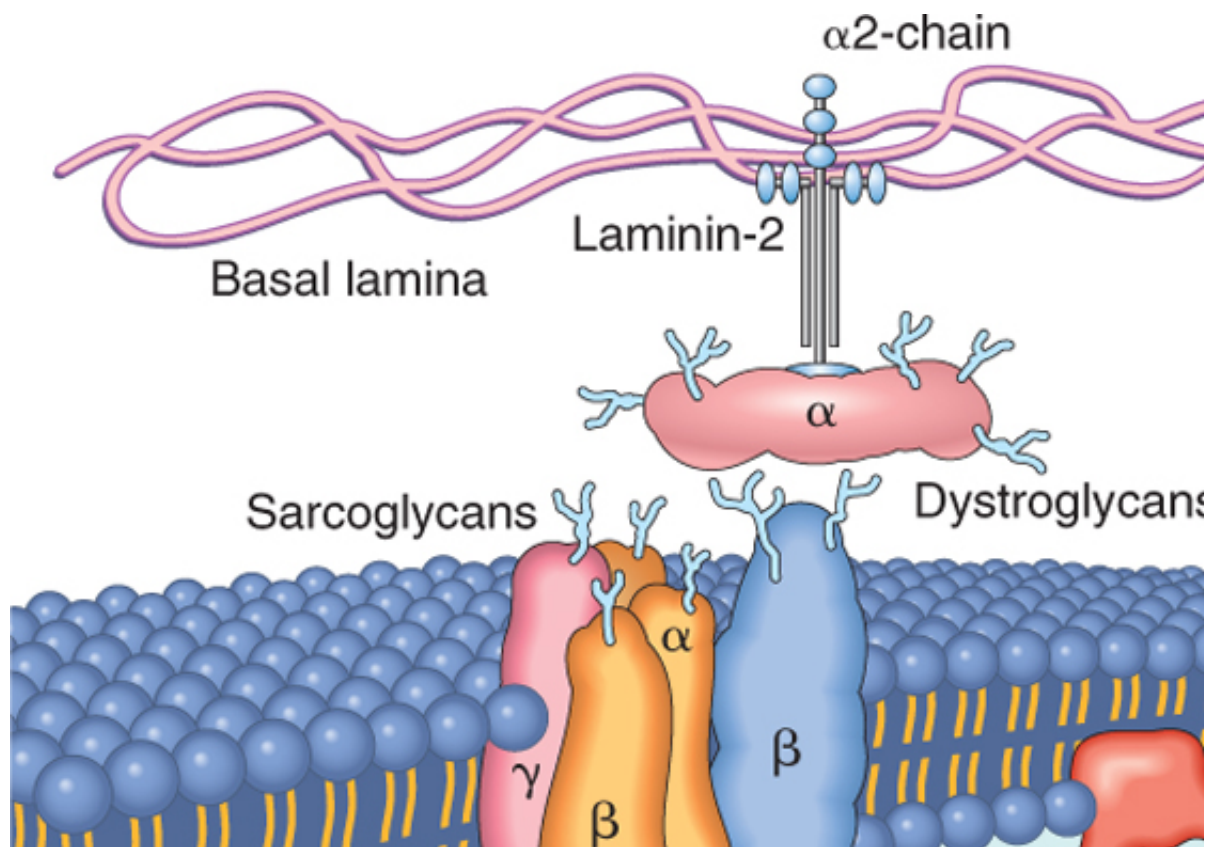
DMD      BMD      Con

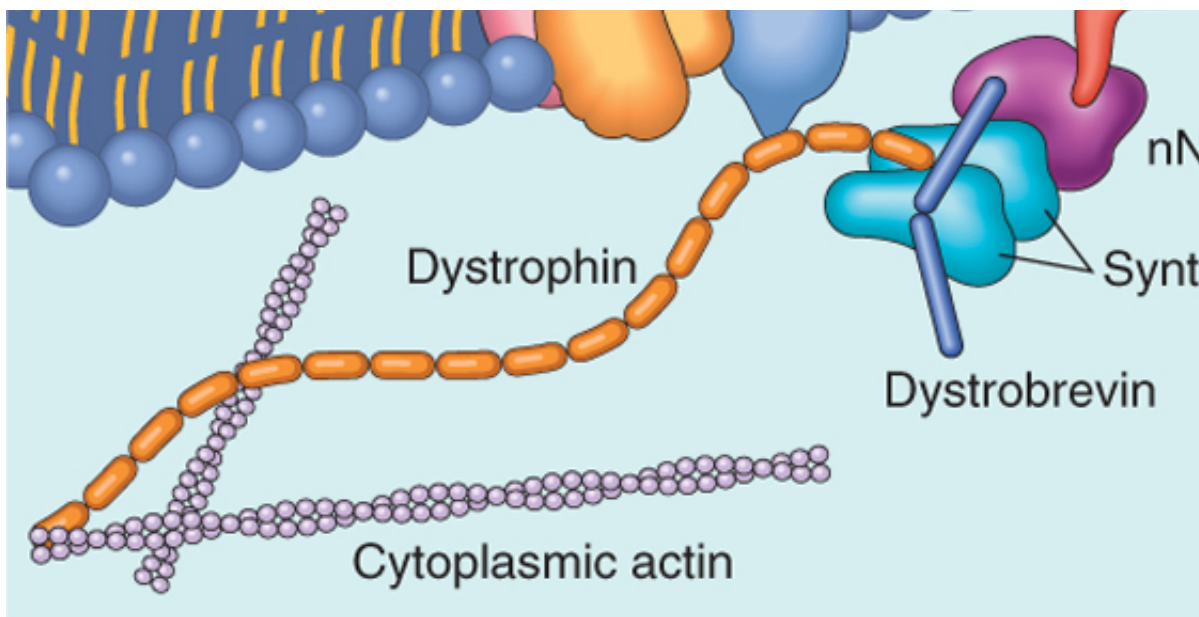




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 Figure 21-23 **A**, Duchenne muscular dystrophy (DMD) showing variation in muscle fiber size, increased endomysial connective tissue, and regenerating fibers (*blue hue*). **B**, Western blot showing absence of dystrophin in DMD and altered dystrophin in Becker muscular dystrophy (BMD) compared with control (Con) (Courtesy of Dr. L. Kunkel, Children's Hospital, Boston, MA)

### Pathogenesis





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Figure 21-24 The relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins. protein, forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans. These transmembrane proteins interact with the ECM, including the laminin proteins. Mutations in dystrophin are a form of muscular dystrophies, mutations in caveolin and the sarcoglycan proteins with the autosomal limb girdle muscular dystrophies, and mutations in the  $\alpha_2$ -laminin (merosin) with a form of congenital muscular dystrophy.

DMD and BMD are caused by abnormalities in the dystrophin gene located on the short arm of the X chromosome (Xp21). Dystrophin is a large protein (427 kD) that is expressed in a wide variety of tissues, including muscle, brain, and peripheral nerves. As shown schematically in Figure 21-24, dystrophin attaches the sarcomere to the cell membrane, maintaining the structural and functional integrity of skeletal muscle. The role of dystrophin in transferring the force of contraction to connective tissue has been proposed as a mechanism for myocyte degeneration that occurs with dystrophin defects, or with changes in other proteins that interact with dystrophin (Fig. 21-24, and see later). Muscle biopsy specimens from individuals with DMD show virtually no immunohistochemical staining or western blot analysis, explaining the greater severity of their presentation (Fig. 21-24B). In comparison, individuals with BMD show diminished amounts of an abnormal molecular weight protein, reflecting mutations that apparently permit limited synthesis of a defective (but still partially active) protein.

The dystrophin gene spans roughly 2400 kilobases (~1% of the total X chromosome), making it one of the largest genes in the human genome; its enormous size is a probable explanation for its particular vulnerability to mutations. To represent a large proportion of the genetic abnormalities, with frameshift and point mutations accounting for approximately two-thirds of the cases are familial, with the remainder representing new mutations. In females, carriers are asymptomatic but often have elevated serum creatine kinase and histologic abnormalities on muscle biopsy. Female carriers, however, are at risk for developing dilated cardiomyopathy.

### Clinical Features

Boys with DMD are normal at birth, and early motor milestones are met on time. Walking, however, is delayed, and the first indications of muscle weakness are clumsiness and inability to keep up with peers. Weakness initially involves the pelvic girdle muscles and then extends to the shoulder girdle. Enlargement of the calf muscles as a result of weakness, a phenomenon termed *pseudohypertrophy*, is an important clinical finding. The increase in size is caused initially by an increase in the size of the muscle fibers and then, as the muscle atrophies, by an increase in connective tissue. Pathologic changes are also found in the heart, and patients may develop arrhythmias. Although there are no well-established structural abnormalities of the central nervous system, cognitive impairment seems to be a component of the disease and is severe enough in some patients to be considered mental retardation. Serum creatine kinase is elevated during the first decade of life but returns to normal levels as the disease progresses, as muscle mass decreases. Death results from respiratory insufficiency, pulmonary infection, or cardiac failure.

decompensation.

Boys with BMD develop symptoms at a later age than those with DMD. The onset occurs in later adolescence, and it is accompanied by a generally slower and more variable rate of progression. The disease is frequently seen in these patients, many have a nearly normal life span.

### Autosomal Muscular Dystrophies

Other forms of muscular dystrophy share many features of DMD and BMD but have distinct clinical characteristics. Some of these muscular dystrophies affect specific muscle groups, and the form is largely on the clinical pattern of muscle weakness. Several autosomal muscular dystrophies affect musculature of the trunk and limbs (similar to the X-linked muscular dystrophies), and are termed *dystrophies*. Limb girdle muscular dystrophies can be inherited either as autosomal dominant or as disorders; six dominant subtypes and ten recessive subtypes have been identified. Mutations of the *complex of proteins* cause four of the recessive forms of these dystrophies (see Fig. 21-24), with one associated with other cytoskeletal proteins or caveolin.

### Myotonic Dystrophy

*Myotonia* is a sustained involuntary contraction of a group of muscles; it is the cardinal neuromuscular feature of myotonic dystrophy. Patients often complain of "stiffness" and have difficulty in releasing their grip handshake. Myotonia can often be elicited by percussion of the thenar eminence.

Myotonic dystrophy is inherited as an autosomal dominant trait; it is associated with a CTG trinucleotide expansion on chromosome 19 that affects the mRNA for the dystrophin myotonia-protein kinase. If fewer than 30 CTG repeats are present; disease develops with expansion of this repeat, and in severe individuals several thousand repeats may be present. Expansion of the trinucleotide repeat influences the concentration of the protein product. Like other "trinucleotide repeat disorders" (e.g., fragile X syndrome; see Chapter 7), myotonic dystrophy tends to increase in severity and appear at a younger age in successive generations, a phenomenon termed *anticipation*. With each new generation there is expansion of the repeat during gametogenesis, and this seems to correspond to the clinical feature of anticipation.

The disease often presents in late childhood with gait abnormalities attributable to weakness of foot muscles; it progresses to weakness of the intrinsic muscles of the hands and wrist extensors; atrophy of facial muscles ensues.

### SUMMARY

**Muscular Dystrophy** Muscular dystrophies are inherited disorders usually manifesting in childhood as skeletal muscular weakness and wasting; cardiac muscle can also be affected with congestive heart failure. The most common muscular dystrophies are X-linked and related to defective synthesis (Duchenne muscular dystrophy) or autosomal recessive forms (Becker muscular dystrophy) of *dystrophin*. Other forms of muscular dystrophy can involve other proteins of the sarcoglycan complex; specific diagnoses strongly depend on the patterns of clinical presentation. Myotonic dystrophy presents with muscle weakness as well as myotonia; the most common form is a trinucleotide repeat disorder affecting the synthesis of an intracellular protein kinase.





## MYOPATHY

The term *myopathy* encompasses a heterogeneous group of disorders, both morphologically and we will segregate these into congenital and toxic (i.e., acquired) forms. Although a complete review recognition of these disorders is important for genetic counseling or appropriate treatment of acqu

### Congenital Myopathies

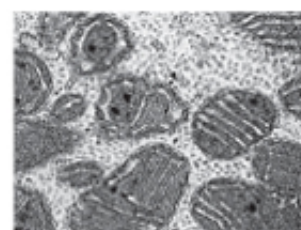
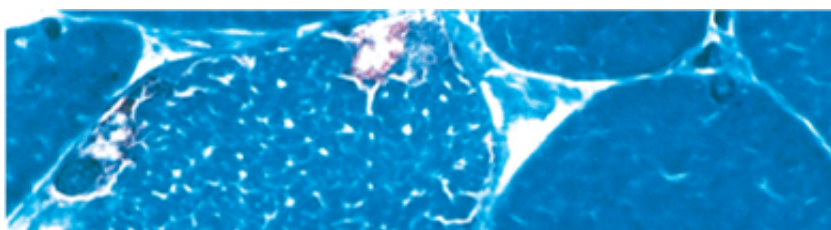
Important subcategories include disorders caused by *inherited mutations of ion channels* (channe exemplified by glycogen and lipid storage diseases), and *mitochondrial abnormalities*.

*Ion channel myopathies* are a group of familial diseases characterized clinically by myoton paralysis (associated with variably abnormal serum potassium concentrations), or both. As caused by mutations in genes that encode ion channels. Thus, *hyperkalemic periodic para* for the skeletal muscle sodium channel protein SCN4A, which regulates sodium entry durir a rare clinical syndrome characterized by a dramatic hypermetabolic state (tachycardia, ta hyperpyrexia) triggered by anesthesia, usually involving halogenated inhalational agents a identified in genes encoding calcium channels. *Myopathies due to inborn errors of metaboli* synthesis and degradation (see [Chapter 7](#)), and abnormalities in lipid handling. Specifically system or deficiencies of the mitochondrial dehydrogenase enzyme systems can lead to si myocytes (*lipid myopathies*). *Mitochondrial myopathies* can involve mutations in either mito mitochondrial constituents. The mitochondrial genome (mtDNA) encodes one-fifth of the pr phosphorylation, as well as 22 mitochondrial-specific tRNAs and 2 rRNA species. Disease inheritance, because only the oocyte contributes mitochondria to the embryo. Mitochondria adulthood with proximal muscle weakness, and sometimes with severe involvement of the *ophthalmoplegia*). There can also be neurologic symptoms, lactic acidosis, and cardiomyo findings in skeletal muscle are irregular muscle fibers and aggregates of abnormal mitocho appearance to the muscle fiber on the modified Gomori trichrome stain, hence the term *rag* electron microscopic appearance is also often distinctive: there are increased numbers of, of mitochondria, some of which contain paracrystalline *parking lot inclusions* or alterations

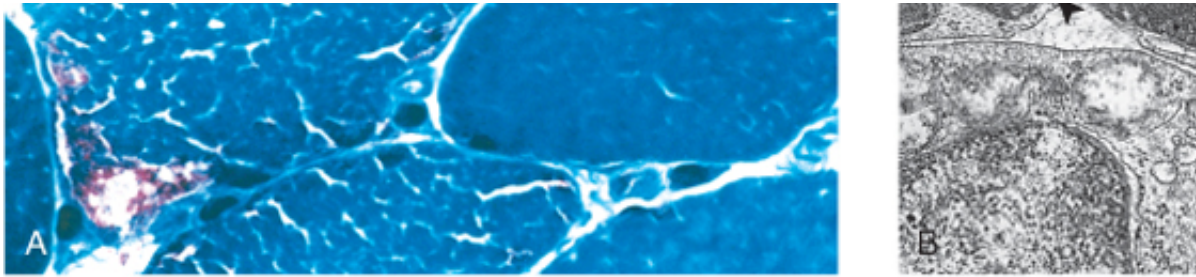
### Toxic Myopathies

Important subcategories include disorders caused by *intrinsic* exposures (e.g. thyroxine) versus e therapeutic drugs).

*Thyrotoxic myopathy* can present as either acute or chronic proximal muscle weakness, ar thyroid dysfunction. Findings include myofiber necrosis, regeneration, and interstitial lymph binge drinking, where there is an acute toxic rhabdomyolysis with accompanying myoglobin Clinically, the patient may acutely develop pain that is either generalized or confined to a s myocyte swelling and necrosis, myophagocytosis, and regeneration. *Chloroquine*<sup>®</sup> can als humans. The most prominent finding is myocyte vacuolization, and with progression, myoc







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 Figure 21-25 **A**, Mitochondrial myopathy showing an irregular fiber with subsarcolemmal collections of mitochondria (ragged red fiber). **B**, Electron micrograph of mitochondria from biopsy specimen in **A** showing numerous small, dark, rounded structures (mitochondria) with prominent cristae.



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## DISEASES OF THE NEUROMUSCULAR JUNCTION

### Myasthenia Gravis

*Myasthenia gravis is an autoimmune disorder of the neuromuscular junction characterized by muscle weakness.* The disease affects roughly 3 in 100,000 persons; it can present at any age and has a predilection for women. Thymic hyperplasia is found in 65% and a thymoma in 15% of patients. Circulating antibodies to the skeletal muscle acetylcholine receptors (AChRs) are present in nearly all patients, associated with a decrease in the number of AChRs. The disease can be transferred to animals with serum from affected patients, demonstrating the causal role of the anti-AChR antibodies.

#### Pathogenesis

In most cases, the autoantibodies against the AChR lead to loss of functional AChRs at the neuromuscular junction either by (1) increasing the internalization and degradation of the receptors, and/or (2) blocking the binding of acetylcholine (ACh) to its receptor. Notably, the autoantibodies do not appear to cause disease by inducing muscle destruction. Despite the evidence that anti-AChR antibodies function critically in the pathogenesis of the disease, antibody levels and neurologic deficit are not always correlated. The link between autoimmunity to AChRs and the thymic abnormalities is also unclear. Nevertheless, most patients show improvement after thymectomy.

#### Clinical Features

Typically, weakness is first noticed in the extraocular muscles; drooping eyelids (*ptosis*) and double vision (*diplopia*) cause the patient to seek medical attention. The generalized muscle weakness can fluctuate dramatically, with alterations occurring over the course of days, hours, or even minutes. Repetitive electrophysiologic stimulation typically elicits diminishing muscle strength, and patients show marked improvement after administration of anticholinesterase agents—the latter presumably by increasing the levels of ACh in the neuromuscular synapse; both maneuvers are diagnostically useful. Sensory and autonomic functions are not affected in myasthenia gravis. Respiratory compromise was a major cause of mortality in the past; 95% of patients now survive more than 5 years after diagnosis because of improved treatment (anticholinesterase drugs, [prednisone](#)<sup>®</sup>, plasmapheresis, and thymic resection), as well as ventilatory support.

### Lambert-Eaton Myasthenic Syndrome

The *Lambert-Eaton myasthenic syndrome* characteristically develops as a paraneoplastic process (see [Chapter 6](#)), most commonly in the setting of small-cell lung carcinoma (60% of cases); it can also occur in the absence of malignancy. Although individuals with Lambert-Eaton syndrome also present with muscle weakness, the syndrome is distinct from myasthenia gravis in several ways: (1) anticholinesterase administration does not improve symptoms; (2) autonomic function is affected; and (3) electrophysiologic studies demonstrate that repeated stimulation elicits *increasing* muscle strength. In these patients, the content of ACh is normal in neuromuscular junction synaptic vesicles, and the postsynaptic membrane is normally responsive to ACh, but fewer vesicles than normal are released in response to each presynaptic action potential. This is attributed to antibodies that recognize presynaptic calcium channels; a similar disease can be transferred to animals with these antibodies.





## SKELETAL MUSCLE TUMORS

Skeletal muscle neoplasms are almost all malignant. The benign rhabdomyoma is rare and will not. *rhabdomyomas* are examples of hamartomas.

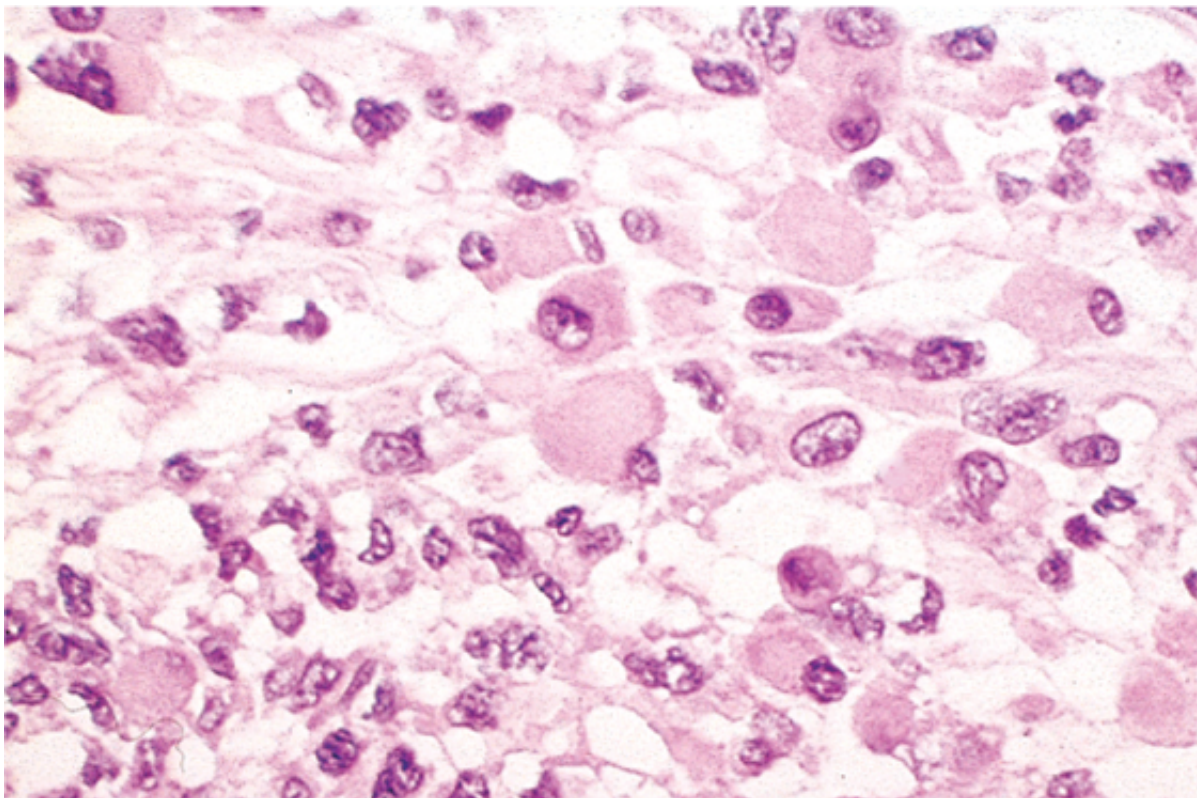
### Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and adolescence, usually. Interestingly, they occur most commonly in the head and neck or genitourinary tract, usually at sites where skeletal muscle is a normal constituent.

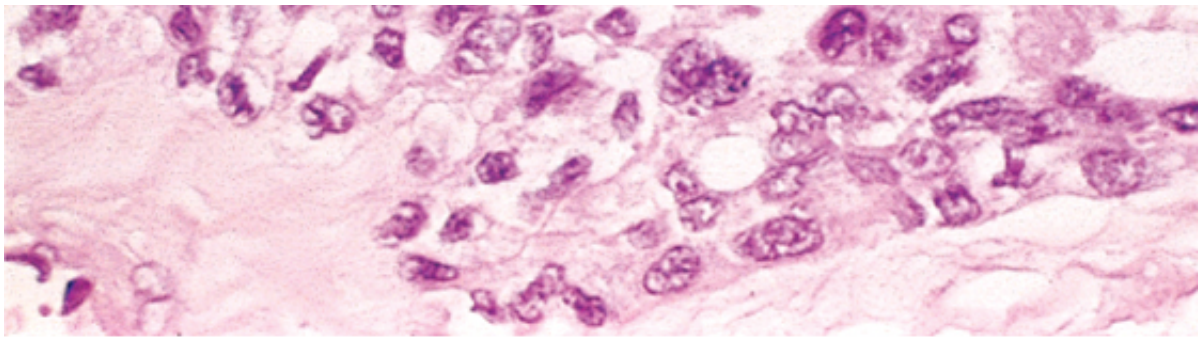
*Chromosomal* translocations are found in most cases; the more common t(2;13) translocation fuses the *FKHR* gene on chromosome 13. *PAX3* functions upstream of genes that control skeletal muscle differentiation; the fusion probably involves dysregulation of muscle differentiation by the chimeric PAX3-FKHR protein.

#### Morphology

The gross appearance of rhabdomyosarcomas is variable. Some tumors, particularly those arising from the mucosal surfaces of the bladder or vagina, can present as soft, gelatinous, grape-like masses. Histologically, they are subclassified into the **embryonal**, **alveolar**, and **pleomorphic** variants. The rhabdomyoblast is the diagnostic cell in all types; it exhibits granular eosinophilic cytoplasm rich in myofibrils. The rhabdomyoblasts may be round or elongated; the latter are known as **tadpole** cells and may contain cross-striations visible by light microscopy. The diagnosis of rhabdomyosarcoma is based on the demonstration of skeletal muscle differentiation, either in the form of sarcomeres on the light microscope or by immunohistochemical demonstration of muscle-associated antigens such as desmin or muscle-specific actin.







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Figure 21-26 Rhabdomyosarcoma. The rhabdomyoblasts are large and round and have abundant eosinophilic cytoplasm.

Rhabdomyosarcomas are aggressive neoplasms treated with a combination of surgery, chemotherapy, and radiation. The histologic variant of the tumor influence survival; embryonal, pleomorphic, and alveolar variants have the worst prognosis. The malignancy is curable in almost two-thirds of children, but adults do much more poorly.



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## SOFT TISSUE TUMORS

By convention, the term *soft tissue* describes any non-epithelial tissue other than bone, cartilage, CNS, hematopoietic, and lymphoid tissues. Soft tissue tumors are classified according to the tissue type they recapitulate, including fat, fibrous tissue, and neurovascular tissue ([Table 21-4](#)). In some soft tissue neoplasms, however, no corresponding normal counterpart is known. With the exception of skeletal muscle neoplasms (see above), benign soft tissue tumors outnumber their malignant counterparts by at least 100 : 1. In the United States, approximately 8000 soft tissue sarcomas are diagnosed annually, representing less than 1% of all invasive malignancies. Nevertheless, they cause 2% of all cancer deaths, reflecting their lethal nature.

Most soft tissue tumors arise without antecedent causes, although rarely radiation, burn injury, or toxin exposure are implicated. Kaposi sarcoma ([Chapter 11](#)) is associated with the human herpesvirus 8, but viruses are probably not important in the pathogenesis of most sarcomas. A small minority of sarcomas are associated with genetic syndromes, most notably neurofibromatosis type 1 (neurofibroma, malignant schwannoma), Gardner syndrome (fibromatosis), Li-Fraumeni syndrome (soft tissue sarcoma), and Osler-Weber-Rendu syndrome (telangiectasia). Specific chromosomal abnormalities and genetic derangements in these syndromes provide important clues about the genesis of the neoplasms. Even in sporadic soft tissue sarcomas, characteristic chromosomal abnormalities can be detected. These provide insight into pathogenesis, as well as diagnostic markers. Some tumors, such as Ewing sarcoma and synovial sarcoma, are eventually defined by their translocation.

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**Table 21-4. Soft Tissue Tumors**

<b>•Tumors of Adipose Tissue</b>
Lipomas
Liposarcoma
<b>•Tumors and Tumor-like Lesions of Fibrous Tissue</b>
Nodular fasciitis
Fibromatoses
Superficial fibromatoses
Deep fibromatoses
Fibrosarcoma
<b>•Fibrohistiocytic Tumors</b>
Fibrous histiocytoma
Dermatofibrosarcoma protuberans
Malignant fibrous histiocytoma
<b>•Tumors of Skeletal Muscle</b>
Rhabdomyoma
Rhabdomyosarcoma
<b>•Tumors of Smooth Muscle</b>
Leiomyoma
Smooth muscle tumors of uncertain malignant potential
Leiomyosarcoma
<b>•Vascular Tumors</b>

Hemangioma
Lymphangioma
Hemangioendothelioma
Hemangiopericytoma
Angiosarcoma
<b>•Peripheral Nerve Tumors</b>
Neurofibroma
Schwannoma
Malignant peripheral nerve sheath tumors
<b>•Tumors of Uncertain Histogenesis</b>
Synovial sarcoma
Alveolar soft part sarcoma
Epithelioid sarcoma
Granular cell tumor

Soft tissue tumors can arise in any location, although approximately 40% occur in the lower extremities, especially the thigh. The incidence generally increases with age, although 15% arise in children. Certain sarcomas tend to appear in certain age groups, e.g., rhabdomyosarcoma in children, synovial sarcoma in young adulthood, and liposarcoma and malignant fibrous histiocytoma in later adult life.

Several features of soft tissue tumors influence prognosis:

*Accurate histologic classification is critical.* Although cell morphology and architectural arrangement are important, these features are often inadequate to distinguish different sarcomas, particularly if they are poorly differentiated. Consequently, immunohistochemistry, electron microscopy, cytogenetics, and molecular genetics are indispensable in assigning the correct diagnosis in some cases. *Sarcoma grade is important for predicting behavior.* Grading, usually I to III, is based on the degree of differentiation, the average number of mitoses per high-power field, cellularity, pleomorphism, and an estimate of the extent of necrosis (presumably a reflection of rate of growth). Mitotic counts and necrosis are the most important predictors. *Staging helps determine the prognosis.* With tumors larger than 20 cm, metastases develop in 80% of cases; in contrast, for tumors 5 cm or smaller, metastases occur in only 30% of cases. In general, tumors arising in superficial locations (e.g., skin) have a better prognosis than deep-seated lesions; overall, the 10-year survival rate for sarcomas is approximately 40%.

With this brief background, we now turn to the individual tumors and tumor-like lesions; only the more common will be covered. Some of the soft tissue tumors are presented elsewhere; we have already discussed some of the joint and skeletal muscle tumors above. Tumors of peripheral nerve are briefly covered in [Chapter 23](#), and tumors of vascular origin, including Kaposi sarcoma, are highlighted in [Chapter 11](#).





## FATTY TUMORS

### Lipoma

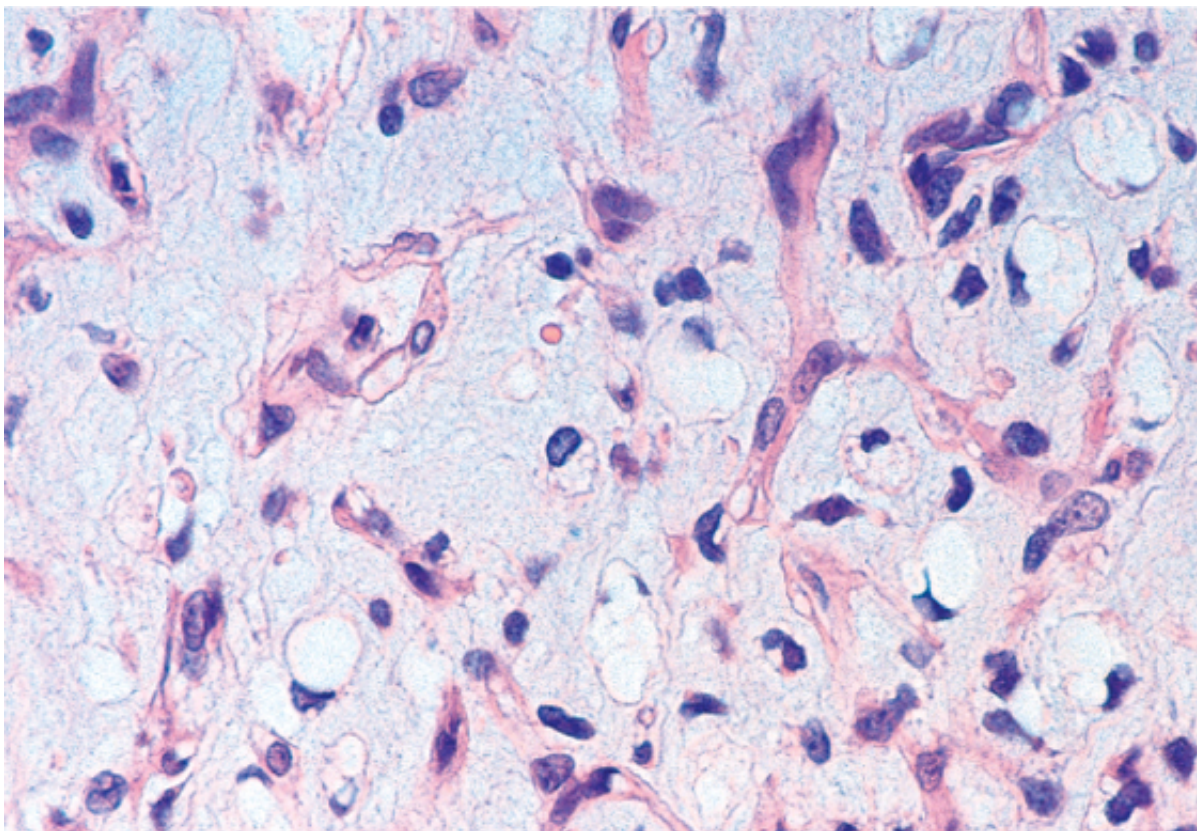
*Lipomas* are benign tumors of fat, and are the most common soft tissue tumors of adulthood. Most lipomas usually suggest the presence of rare autosomal dominant syndromes. Lipomas can be several features (e.g., conventional, myolipoma, spindle cell, myelolipoma, pleomorphic, angiolipoma), and chromosomal rearrangements. Most lipomas are mobile, slowly enlarging, painless masses (angiolipomas can be painful). Treatment is usually curative.

#### Morphology

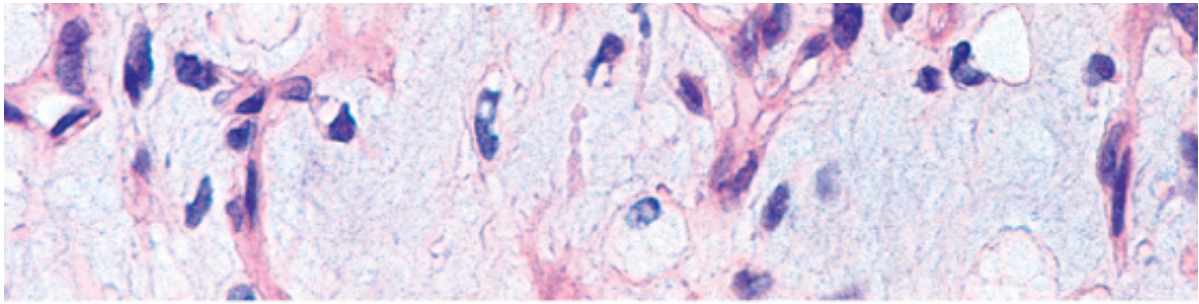
**Conventional lipomas** (the most common subtype) are soft, yellow, well-encapsulated masses of mature adipocytes; they can vary considerably in size. Histologically, they consist of mature adipocytes with minimal pleomorphism.

### Liposarcoma

*Liposarcomas* are malignant neoplasms of adipocytes. They occur most commonly in the fifth and sixth decades of life, and arise in the deep soft tissues or in visceral sites. The prognosis of liposarcomas is greatly influenced by histologic subtype, and myxoid variants tend to grow in a fairly indolent fashion and have a more favorable outlook than pleomorphic variants, which tend to recur after excision and metastasize to lungs. Amplification of the *MDM2* gene is characteristic of well-differentiated liposarcomas; this region contains the *MDM2* gene whose product binds to and inactivates the *p53* protein. A reciprocal chromosomal translocation is associated with myxoid liposarcomas and with some cases of round cell liposarcoma, which affects a transcription factor that plays a role in normal adipocyte differentiation.







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 Figure 21-27 Myxoid liposarcoma. Adult-appearing fat cells and more primitive cells, with lipid vacuoles (*lipoblasts*)

### Morphology

Liposarcomas usually present as relatively well-circumscribed lesions. Several different types are recognized, including two low-grade variants, the **well-differentiated liposarcoma** and the **myxoid liposarcoma**, the latter characterized by abundant, mucoid extracellular matrix. Some lesions can be difficult to distinguish histologically from lipomas, whereas very poorly differentiated liposarcomas can resemble various other high-grade malignancies. In most cases, cells indicative of liposarcoma are present. Such cells are known as **lipoblasts**; they recapitulate fetal fat cells with cytoplasmic lipid that scallop the nucleus (Fig. 21-27).



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## FIBROUS TUMORS AND TUMOR-LIKE LESIONS

Fibrous tissue proliferations are a heterogeneous group of lesions. At one end of the spectrum, *nodular fasciitis* is a reactive, self-limited proliferation. At the other end, *fibrosarcomas* are highly malignant neoplasms that can metastasize. *Fibromatoses* fall somewhere in the middle; these are characterized as benign lesions with local growth and can defy adequate surgical excision. Distinguishing the various lesions requires a large part of the pathologist.

### Reactive Proliferations

#### ***Nodular Fasciitis***

Nodular fasciitis is a self-limited, reactive fibroblastic proliferation that typically occurs in adults on the trunk, most frequently by the chest and back. Patients characteristically present with a several-week history of a painless, occasionally painful mass. Preceding trauma is noted in 10% to 15% of cases. Lesions of nodular fasciitis are usually well-circumscribed.

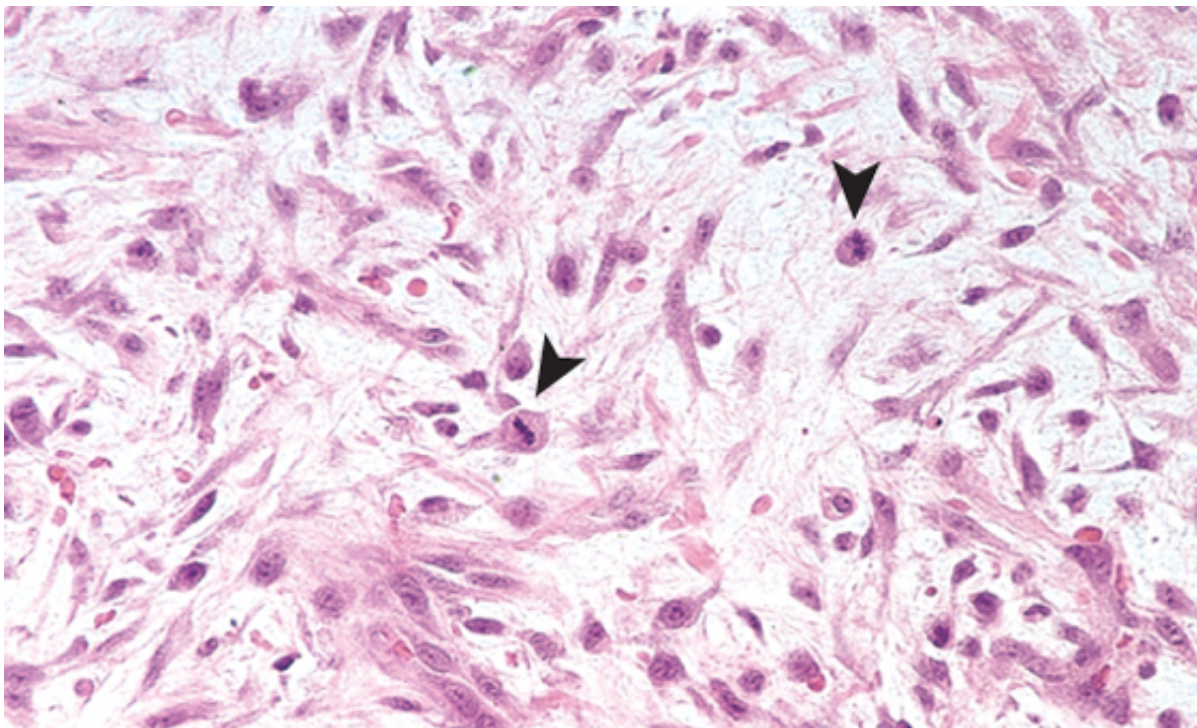
#### **Morphology**

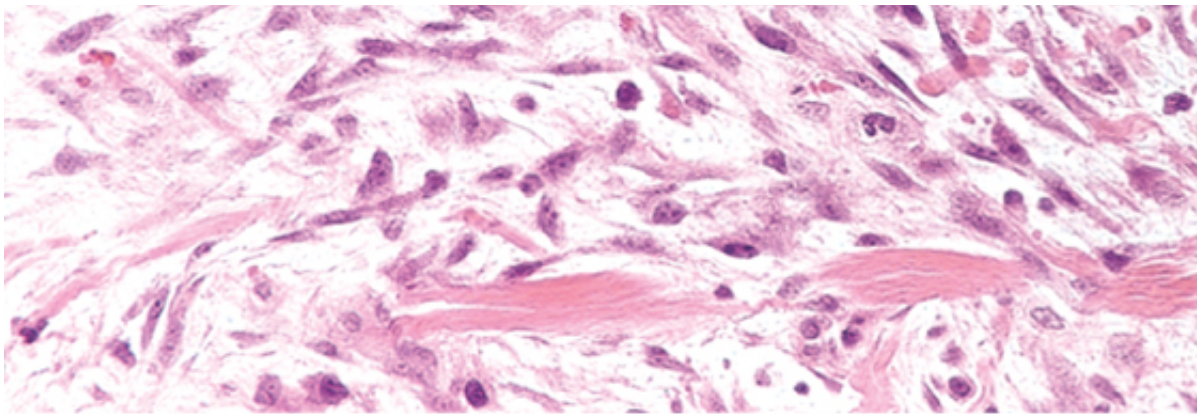
Characteristically, the lesion is several centimeters in greatest dimension and nodular with ill-defined margins. Histologically, it is richly cellular and consists of plump, randomly arranged fibroblasts in an abundant myxoid stroma (Fig. 21-28). The cells vary in size and shape and have conspicuous nucleoli and numerous mitoses.

#### ***Myositis Ossificans***

Myositis ossificans is distinguished from other fibroblastic proliferations by the presence of *metaplastic bone* in the proximal muscles of the extremities in athletic adolescents and young adults after trauma. The lesion eventually evolves into a painless, hard, well-demarcated mass. It is critical to distinguish the lesion from a soft tissue sarcoma. Simple excision of myositis ossificans is usually curative.

#### **Fibromatoses**





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Figure 21-28 Nodular fasciitis. A highly cellular lesion composed of plump, randomly oriented spindle cells surrounding a central area of activity (arrowheads).

The fibromatoses are a group of fibroblastic proliferations distinguished by their tendency to grow in recurrent cases, to recur after surgical removal. Although some lesions are *locally aggressive*, they do not metastasize. They are divided into two major clinicopathologic groups: superficial and deep.

The *superficial fibromatoses* arise in the superficial fascia and include such entities as palmar and penile fibromatosis (*Peyronie disease*). Superficial lesions are genetically distinct from deep lesions; they are generally more innocuous (they can be associated with trisomy 3 and 8); they also come to cause deformity of the involved structure. The *deep fibromatoses* include the so-called *desmoid tumors*, which arise in the connective tissue wall and muscles of the trunk and extremities, and within the abdomen (mesentery and pelvis). A component of *Gardner syndrome*, an autosomal dominant disorder including colonic adenomatous polyposis, is a component of *Gardner syndrome*, an autosomal dominant disorder including colonic adenomatous polyposis. Mutations in the *APC* or  $\beta$ -catenin genes are present in the majority of these tumors. Deep lesions are more aggressive, recur after excision.

### Morphology

These tumors are gray-white, firm to rubbery, poorly demarcated, infiltrative masses of variable dimension. Histologically, fibromatoses are composed of plump cells arranged in bundles that penetrate the adjacent tissue; mitoses are infrequent. Immunohistochemical analysis shows that these cells are probably **myofibroblasts**. Some lesions may be quite cellular, while others are less so. In their evolution, whereas others, especially the superficial fibromatoses, contain abundant collagen.

In addition to being disfiguring or disabling, fibromatoses are occasionally painful. Although curable, they recur when incompletely removed. Some tumors respond to tamoxifen, and in other cases chemotherapy. Reports of metastases likely represent misdiagnosis of an original fibrosarcoma.

### Fibrosarcoma

Fibrosarcomas are malignant neoplasms composed of fibroblasts. Most occur in adults, typically in the retroperitoneal area. They tend to grow slowly, and have usually been present for several years before diagnosis. As with sarcomas, fibrosarcomas often recur locally after excision (>50% of cases) and can metastasize to the lungs.

### Morphology

Fibrosarcomas are soft unencapsulated, infiltrative masses frequently with areas of necrosis. Better differentiated lesions can appear deceptively encapsulated. Histologically, they range from all degrees of differentiation, from tumors that closely resemble fibromatosis, to dedifferentiated sarcomas with spindled cells growing in a herringbone fashion (Fig. 21-29), to highly cellular neoplasms with marked architectural disarray, pleomorphism, frequent mitoses, and necrosis.



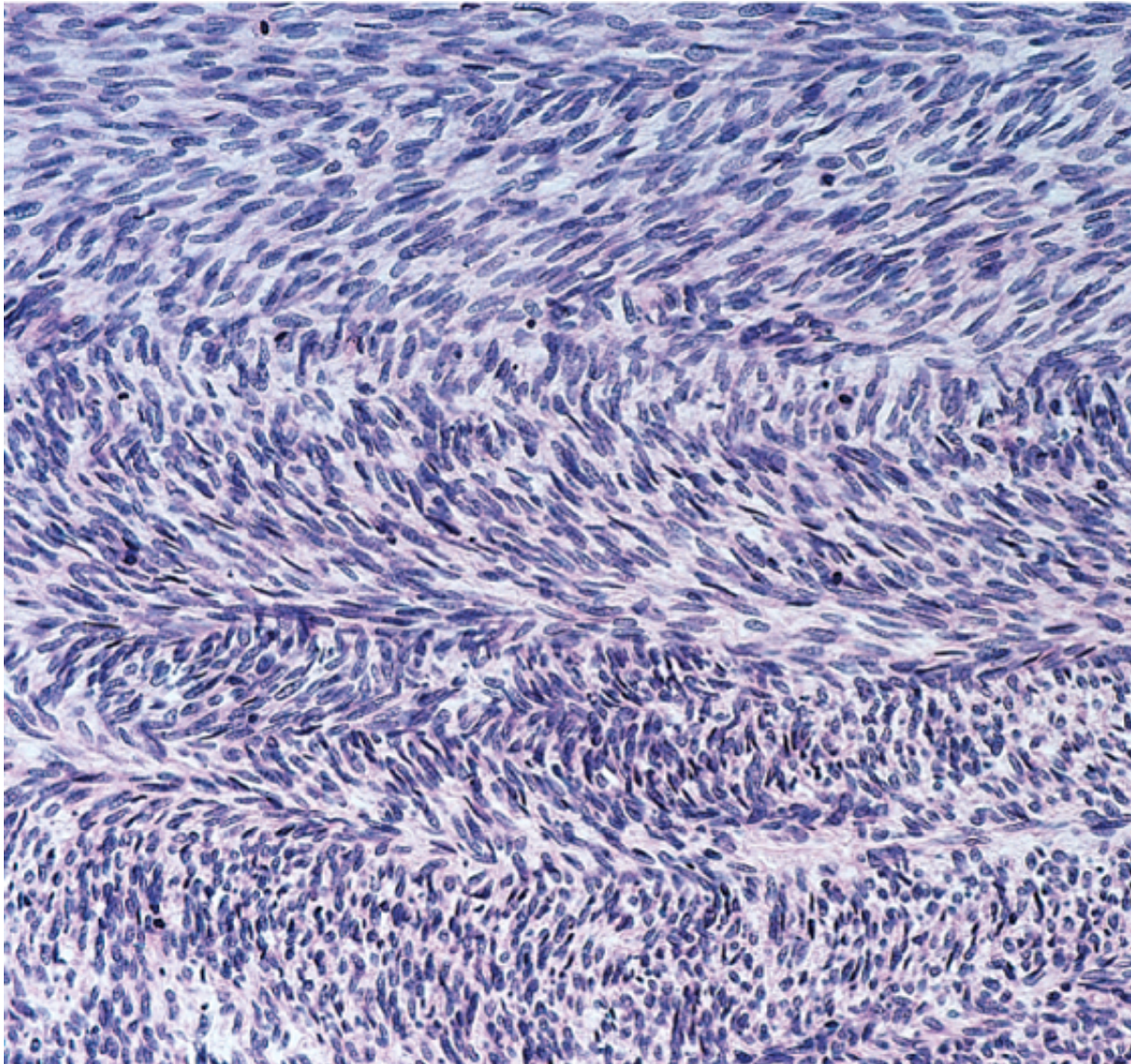
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## FIBROHISTIOCYTIC TUMORS



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Figure 21-29 Fibrosarcoma. Malignant spindle cells here are arranged in a herring

Fibrohistiocytic tumors are composed of a mixture of fibroblasts and phagocytic, lipid-laden cells. Neoplastic cells in many cases are most likely fibroblasts. Nevertheless, detailed immunohistochemical studies have shown that a significant number of such tumors actually derive from other cell types. Consequently, the term *fibrohistiocytic* malignant variants, should be considered descriptive and not necessarily connoting a specific cell type. The range of histologic patterns and biologic behavior, from self-limited benign lesions to high-grade sarcomas, is broad.

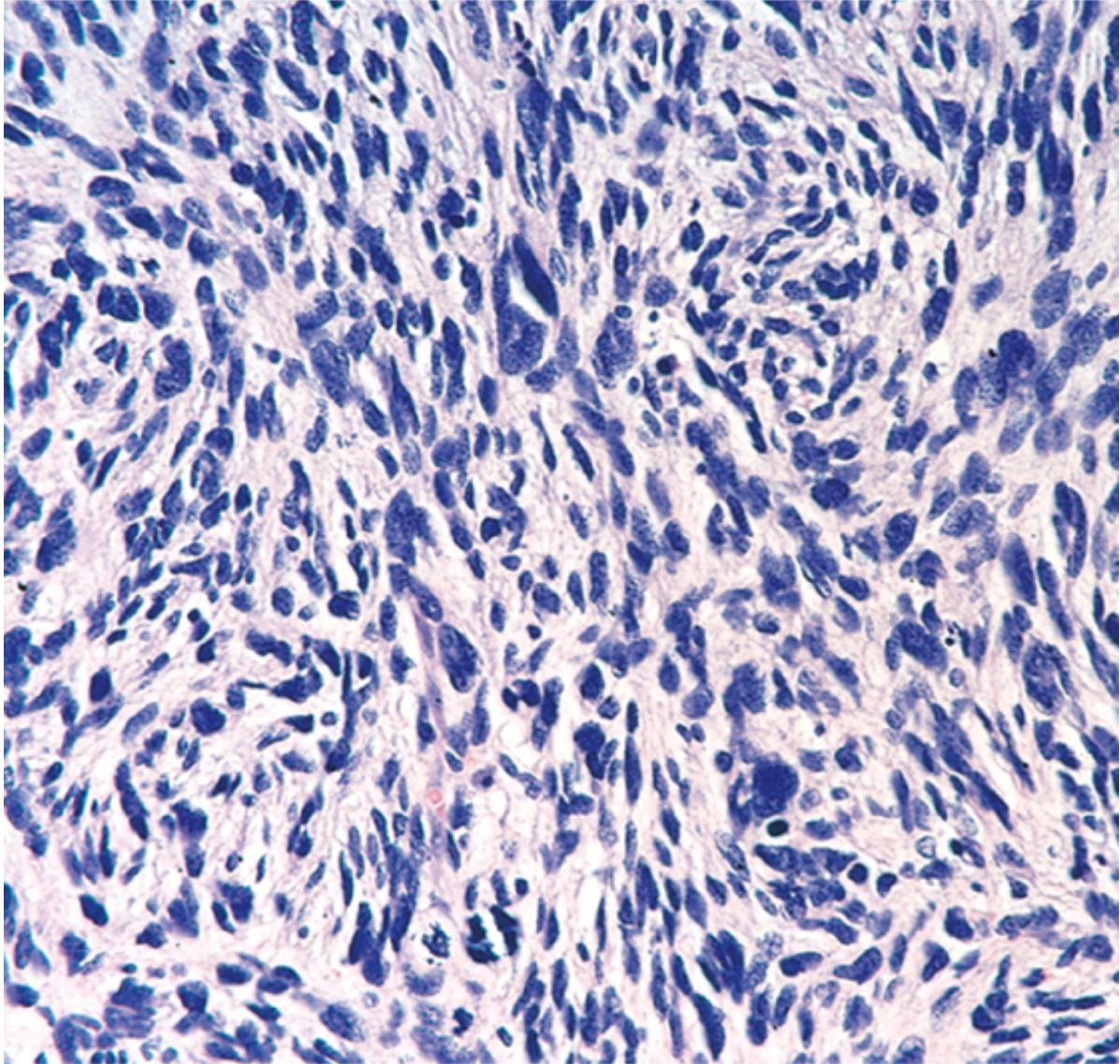
### Benign Fibrous Histiocytoma (Dermatofibroma)

Dermatofibromas are relatively common benign lesions in adults presenting as circumscribed, small nodules in the dermis or subcutaneous tissue. Histologically, these typically consist of bland, interlacing spindle cells and collagen bundles. The borders of the lesions tend to be infiltrative, but extensive local invasion does not occur.



pathogenesis of these lesions is uncertain.

### **Malignant Fibrous Histiocytoma**



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Figure 21-30 Malignant fibrous histiocytoma. There are fascicles of plump spindle cells in a swirling (storiform) pattern (H&E, 100x). (From Kumar et al, Robbins Basic Pathology, 8e, 2010, Women's Hospital, Boston, Massachusetts.)

*Malignant fibrous histiocytoma (MFH)* is a term rather loosely applied to a variety of soft tissue sarcomas. It is characterized by cytologic pleomorphism, the presence of bizarre multinucleate cells, and storiform architecture (Figure 21-30). The phenotype of many such tumors is fibroblastic and not histiocytic. Nevertheless, it is also important to recognize that MFH actually exhibit markers for cells of other origin (e.g., smooth muscle cells, adipocytes, skeletal muscle cells, etc.) and are more appropriately classified as leiomyosarcomas, liposarcomas, and the like. Alternatively, some tumors are so poorly differentiated that they do not express any discernible precursor phenotype. Consequently, the classification of MFH is confounded by the extremely heterogeneous collection of tumors that have this name. Indeed, if a cell of origin *can* be established, the tumors tend to behave like others of that same classification. Tumors of fibroblastic differentiation are usually large (5-20 cm), gray-white unencapsulated masses that often recur locally. They usually arise in the musculature of the proximal extremities or in the retroperitoneum. Most recur unless widely excised, and have a metastatic rate of 30% to 50%.

recur unless widely excised, and have a metastatic rate of 50 % to 50 %.



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## SMOOTH MUSCLE TUMORS

### Leiomyoma

Benign smooth muscle tumors, or *leiomyomas*, are common, well-circumscribed neoplasms that can arise from smooth muscle cells anywhere in the body, but are encountered most commonly in the uterus (see [Chapter 19](#)).

### Leiomyosarcoma

Leiomyosarcomas comprise 10% to 20% of soft tissue sarcomas. They occur in adults, more commonly females. Skin and deep soft tissues of the extremities and retroperitoneum are common sites. They commonly present as firm, painless masses; retroperitoneal tumors can be large and bulky and cause abdominal symptoms. Histologically, they show spindle cells with cigar-shaped nuclei arranged in interweaving fascicles. Treatment depends on the size, location, and grade of the tumor. Superficial or cutaneous leiomyosarcomas are usually small and have a good prognosis, whereas retroperitoneal tumors are large, cannot be entirely excised, and cause death by both local extension and metastatic spread.







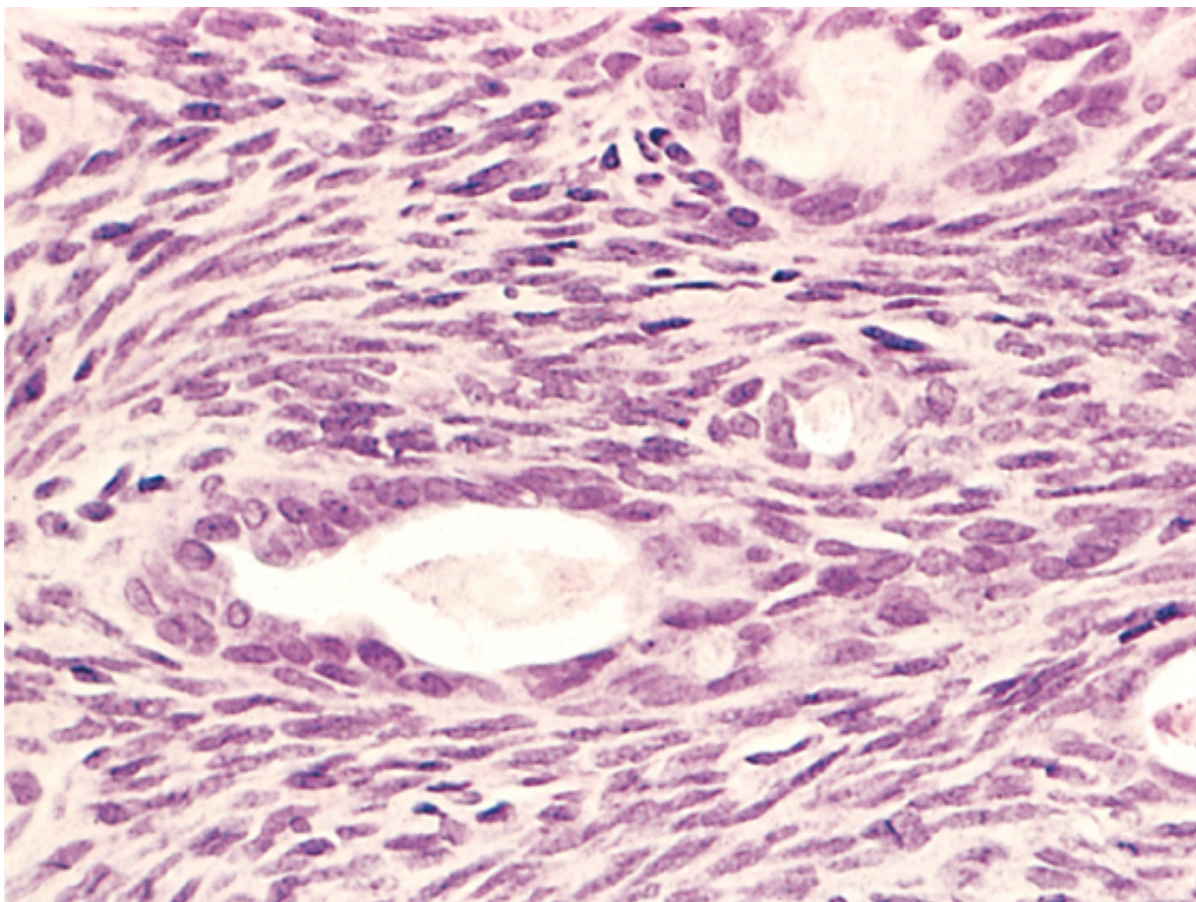
## SYNOVIAL SARCOMA

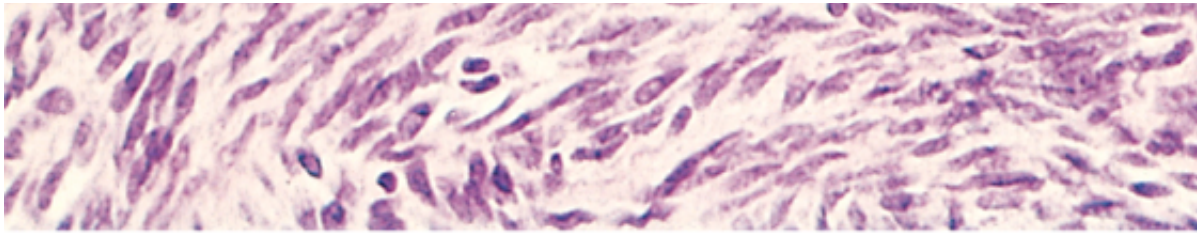
Synovial sarcoma was originally believed to recapitulate synovium; however, the cell of origin is unknown. Reflecting a non-joint origin, less than 10% of synovial sarcomas are intra-articular. It accounts for approximately 10% of all soft tissue sarcomas, typically occurring in individuals in their 20s to 40s around the large joints of the extremities, with 60% to 70% occurring around the knee; many have a long time of presentation. Most synovial sarcomas show a characteristic t(X;18) translocation that produces a fusion gene (encoding a transcription factor) with either SSX1 or SSX2 genes (encoding transcription factors that relate to prognosis).

### Morphology

Histologically, synovial sarcomas may be biphasic or monophasic. Classic **biphasic** synovial sarcoma exhibits differentiation of tumor cells into both epithelial-like cells and spindle cells. The epithelial cells are cuboidal to columnar and form glands or grow in solid cords or aggregates. The spindle cells form densely cellular fascicles that surround the epithelial cells (Fig. 21-31). Many synovial sarcomas are **monophasic**, that is, composed of spindled cells or, rarely, epithelial cells only. Because the spindle cells are easily mistaken for fibrosarcomas or malignant peripheral nerve sheath tumors, immunohistochemistry is helpful, because the tumor cells are positive for keratin antigen, differentiating them from most other sarcomas.

Synovial sarcomas are treated aggressively with limb-sparing surgery and chemotherapy. Commonly, regional lymph nodes are removed. The 5-year survival rate varies from 25% to 62%, and only 10% to 30% live





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Figure 21-31 Synovial sarcoma exhibiting a classic biphasic spindle cell and gland-like t

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## 22 The Skin

ALEXANDER J.F. LAZAR MD, PhD\*

Cutaneous disorders are extremely common and range from irritating acne to life-threatening melanoma. Many cutaneous disorders are intrinsic to the skin, but some are manifestations of systemic disease. Among this latter group are systemic lupus erythematosus, acquired immunodeficiency syndrome (e.g., Kaposi sarcoma), and genetic syndromes such as neurofibromatosis and Muir-Torre syndrome. Thus, skin provides a uniquely accessible window for the recognition of numerous and varied disorders.

Skin is not merely a passive, protective mantle, but rather a complex organ—the largest of the body—with regulated cellular and molecular events that govern interactions with the external environment. Skin is constantly bathed with microbial and nonmicrobial antigens that are processed by bone marrow-derived dendritic Langerhans cells, which in turn communicate with the immune system by migrating to regional lymph nodes. Squamous cells (keratinocytes) help maintain skin homeostasis by secreting a plethora of cytokines that not only regulate interactions among the epidermal cells but also diffuse into and influence the dermal microenvironment. The dermis contains both CD4<sup>+</sup> helper and CD8<sup>+</sup> cytotoxic T lymphocytes; some of these T cells home selectively to the skin by virtue of homing receptors called the cutaneous lymphocyte antigen (CLA). The epidermis contains intraepithelial lymphocytes, including  $\gamma/\delta$  T cells. All these cells are rich sources of cytokines. The local tissue response involving these T cells and cytokines accounts for the microscopic patterns and clinical expressions of cutaneous inflammatory and infectious disease. These patterns can be recognized and interpreted through the microscope by the experienced observer.

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This chapter focuses on diseases of the skin that are common and/or illustrative. The practice of dermatopathology is unique in its close interaction with clinicians (particularly dermatologists, who spend considerable time studying skin pathology in their training) and reliance on clinical presentation and history to render a diagnosis. In effect, the clinical assessment of the condition involving the patient's skin is the gross examination that is subsequently correlated with the microscopic findings to make a diagnosis. Diseases of the skin can be perplexing, because dermatologists and dermatopathologists have a large and unique lexicon not commonly used in describing lesions in other tissues. Because knowledge of dermatologic terms and disease forms the basis of clear understanding and communication, some of these are defined below.

### Macroscopic Terms

**Macule:** Flat, circumscribed area of any size distinguished from surrounding skin by coloration  
**Papule:** Elevated solid area 5 mm or less in diameter  
**Nodule:** Elevated solid area more than 5 mm in diameter  
**Plaque:** Elevated flat-topped area, usually more than 5 mm in diameter  
**Vesicle:** Fluid-filled raised area 5 mm or less in diameter  
**Bulla:** Fluid-filled raised area more than 5 mm in diameter; a large vesicle  
**Blister:** Common term used for vesicle or bulla  
**Pustule:** Discrete, pus-filled raised area  
**Scale:** Dry, horny, platelike excrescence; usually the result of imperfect cornification  
**Lichenification:** Thickened and rough skin characterized by prominent skin markings; usually the result of repeated rubbing in susceptible persons (see "[Lichen Simplex Chronicus](#)")  
**Excoriation:** A traumatic lesion characterized by breakage of the epidermis, causing a raw linear area usually due to scratching.

### Microscopic Terms

• • • • •



**Hyperkeratosis:** Hyperplasia of the stratum corneum, often associated with a qualitative abnormality of the keratin  
**Parakeratosis:** Mode(s) of keratinization characterized by retention of the nuclei in the stratum corneum; on mucosal membranes, parakeratosis is normal.  
**Acanthosis:** Epidermal hyperplasia preferentially involving the stratum spinosum  
**Dyskeratosis:** Abnormal keratinization occurring prematurely within individual cells or groups of cells below the stratum granulosum  
**Acantholysis:** Loss of intercellular connections resulting in lack of cohesion between keratinocytes  
**Papillomatosis:** Hyperplasia of the papillary dermis with elongation and/or widening of the dermal papillae  
**Lentiginous:** Refers to a linear pattern of melanocyte proliferation within the epidermal basal cell layer; lentiginous melanocytic hyperplasia can occur as a reactive change or as part of a neoplasm of melanocytes  
**Spongiosis:** Interstitial edema of the epidermis





## ACUTE INFLAMMATORY DERMATOSES

Literally thousands of specific inflammatory dermatoses exist, hence the clinical variants and nomenclature are challenging to master at any stage of training. In general, acute lesions last from days to weeks and are characterized by inflammation (unlike other tissues, these are often marked by mononuclear cells rather than neutrophils and defined as acute because of the limited course of their natural history), edema, and sometimes epidermal, vascular, or subcutaneous injury. Some acute lesions may persist, resulting in transition to a chronic phase, while others are characteristically self-limited and never progress.

### Urticaria

Urticaria (hives) is a common disorder mediated by *localized mast cell degranulation resulting in dermal microvascular hyperpermeability*. This gives rise to erythematous, edematous, and pruritic plaques termed *wheals*.

#### Pathogenesis

In most cases, urticaria results from antigen-induced release of vasoactive mediators from mast cell granules via sensitization with specific immunoglobulin E (IgE) antibodies (type I hypersensitivity; [Chapter 5](#)). This IgE-dependent degranulation can follow exposure to a number of antigens including pollens, foods, drugs, and insect venom. IgE-independent urticaria may result from substances that directly incite mast cell degranulation, such as opiates and certain antibiotics. In the vast majority of cases, no clinical cause is discovered despite extensive searching. Hereditary angioneurotic edema results from inherited deficiency of C1 esterase inhibitor, yielding uncontrolled activation of the early components of the complement system ([Chapter 2](#)). The resulting urticaria affects the lips, throat, eyelids, genitals, and distal extremities. When the larynx is affected it can be dangerous since airway patency may be compromised.

#### Morphology

The histologic features of urticaria are often subtle with very sparse superficial perivenular infiltrate of mononuclear cells and rare admixed neutrophils. Scattered eosinophils may be present. Superficial dermal edema results in more widely spaced collagen bundles. Degranulation of mast cells, that normally reside around superficial dermal venules, is often not prominent in routine H & E stains, but these can sometimes be highlighted using a Giemsa stain.

#### Clinical Features

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Urticaria generally occurs between the ages of 20 and 40 years. Individual lesions develop and fade within hours (usually <24 hours), but episodes may persist for days or even months. Persistent lesions are sometimes due to urticarial vasculitis associated with temporary vascular damage. Lesions vary from small, pruritic papules to large edematous plaques with erythema resulting from superficial vascular dilation. Increased vascular permeability leads to localized dermal edema. Sites include any area exposed to pressure, such as the trunk, distal extremities, and ears. In general, this condition is more irritating and embarrassing than life-threatening and is managed with antihistamines or steroids in more severe cases.

### Acute Eczematous Dermatitis

*Eczema* is a clinical term that embraces a number of conditions with different underlying

etiologies. All are characterized by red, *papulovesicular, oozing, and crusted lesions* at an early stage. The degree of these changes varies with clinical subtype. With persistence, these lesions develop into raised, *scaling plaques*. Clinical differences permit classification of eczematous dermatitis into: (1) allergic contact, (2) atopic, (3) drug-related eczematous, (4) photoeczematous, and (5) primary irritant forms. Most of these forms resolve completely when the offending stimulus is removed or exposure to it is limited, thus stressing the importance of investigating the underlying cause. Only the most common form, contact dermatitis, will be discussed here.

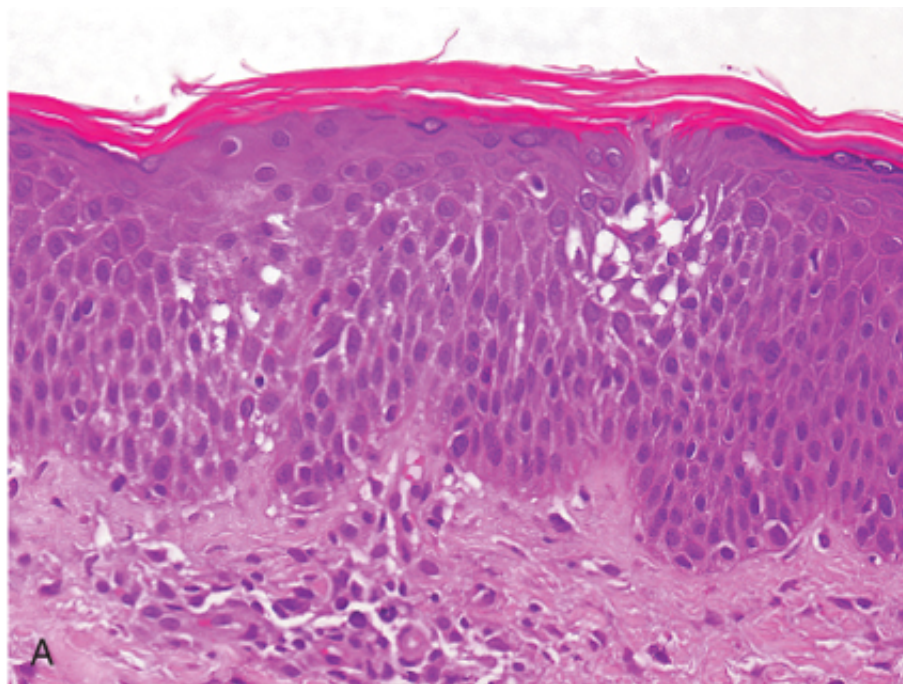
### *Pathogenesis*

After initial exposure to an environmental contact sensitizing agent, such as poison ivy, self-proteins modified by the agent are processed by epidermal Langerhans cells that then migrate to draining lymph nodes and present the antigen to naive T cells. This sensitization event leads to acquisition of immunologic memory; on re-exposure to the antigen, the now-educated CD4<sup>+</sup> T lymphocytes migrate to the affected skin sites. Here they release cytokines that recruit additional inflammatory cells and also mediate the epidermal damage as in any delayed-type hypersensitivity reaction ([Chapter 5](#)).

### **Morphology**

**Spongiosis**-the accumulation of edema fluid within the epidermis-characterizes all forms of acute eczematous dermatitis-hence the synonym "**spongiotic dermatitis**." Edema seeps into the intercellular spaces of the epidermis, splaying apart keratinocytes. Intercellular bridges are stretched and become more prominent visually, giving a "spongy" appearance ([Fig. 22-1A](#)). This is accompanied by a superficial perivascular lymphocytic infiltrate, papillary dermal edema, and mast cell degranulation. Eosinophils may be present and especially prominent in spongiotic eruptions provoked by drugs, but in general there are no specific features for differentiating the various causes of eczema and careful clinical correlation is needed.

### *Clinical Features*





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 Figure 22-1 Eczematous dermatitis. **A**, Fluid accumulation between epidermal cells results in spongiosis that can proceed to small vesicles if intercellular connections are stretched until broken—thus the term spongiotic dermatitis. **B**, Note the patterned erythema and scale associated with nickel contact dermatitis resulting from this woman's necklace.

Lesions of acute eczematous dermatitis are pruritic (itchy), edematous, oozing plaques, often containing vesicles and bullae. With persistent antigen stimulation, lesions may become progressively scaly (hyperkeratotic) as the epidermis thickens (acanthosis) and can become chronic. Some of these changes also result from scratching or rubbing of the lesion (see "Lichen Simplex Chronicus"). The clinical causes of eczema are sometimes divided into "inside" and "outside" jobs—disease resulting from external application of antigen (such as poison ivy) or reaction to an internal circulating antigen (such as ingested food or drug).

Susceptibility to atopic dermatitis is often inherited and this form can be more chronic, although it sometimes improves with age. Atopic individuals often suffer from asthma as well (Chapter 5), perhaps another expression of an irritable and overactive immune system.

### Erythema Multiforme

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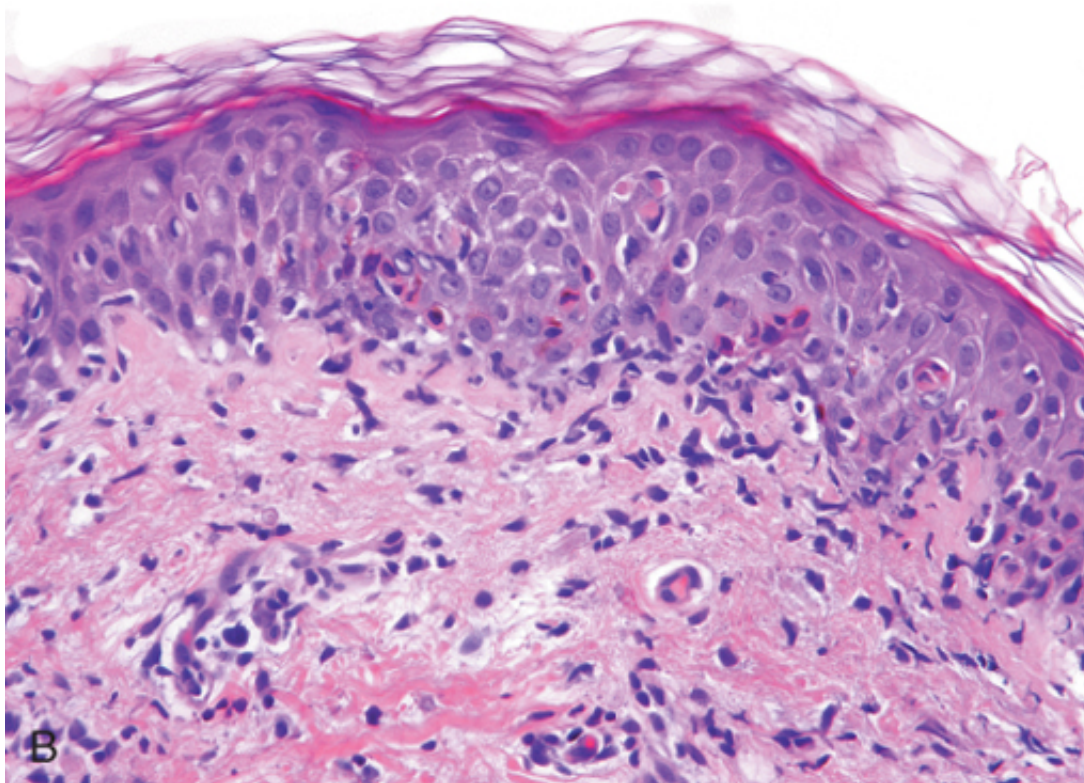
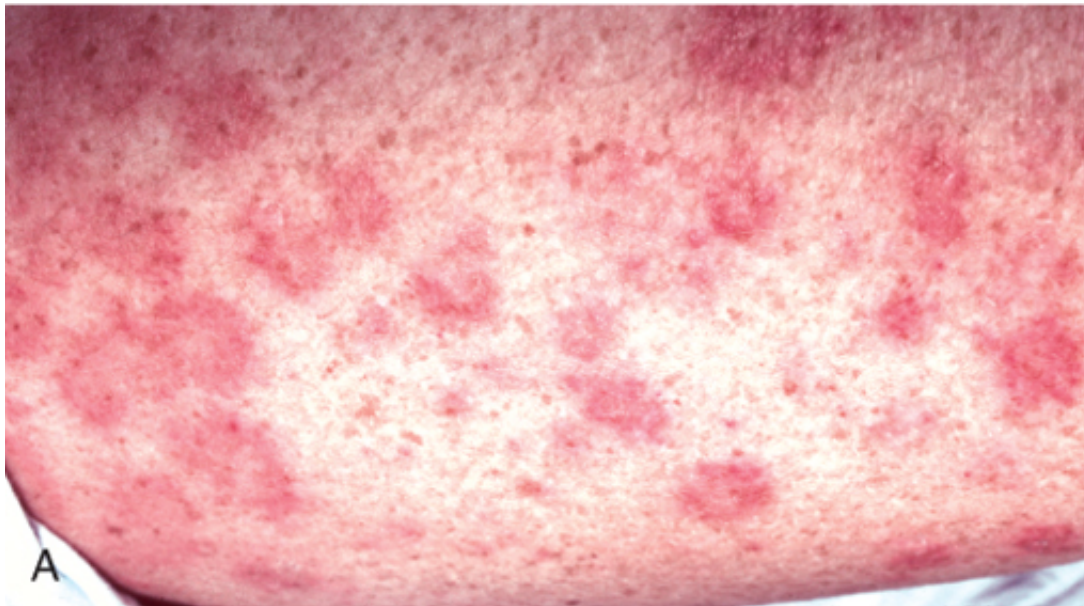
Erythema multiforme is an uncommon, usually self-limited disorder that seems to be a *hypersensitivity response to certain infections and drugs*. Among antecedent infections are those caused by herpes simplex, mycoplasmas, and fungi such as *Histoplasma Capsulatum*, and *Coccidioides immitis*. The implicated drugs include sulfonamides, penicillin, salicylates, hydantoins, and antimalarials. Patients present with an array of "multiform" lesions, including macules, papules, vesicles, and bullae, as well as the characteristic targetoid lesion consisting of a red macule or papule with a pale vesicular or eroded center (Fig. 22-2A).

### Pathogenesis

The lesions of erythema multiforme result from the action of CLA positive, skin-homing cytotoxic T cells that are concentrated in the central portion of the lesions, while CD4+ helper



and Langerhan cells are more prominent in the raised, erythematous periphery. The cytotoxic cells directed against an inciting drug or microbe presumably respond to cross-reactive antigens of the basal cell layer of skin and mucosae and damage these tissues.



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 Figure 22-2 Erythema multiforme. **A**, Lesions show a central zone of dusky pink-gray discoloration that correlates with epidermal necrosis or early blister formation, surrounded by a pink-red rim, producing the characteristic target-like appearance of erythema multiforme minor. **B**, Early lesions show alignment of lymphocytes along the dermoepidermal junction with injury to basal epidermal cells as a result of the cytotoxic assault. This is an interface dermatitis (there is destruction of cells at the epidermal-dermal interface), but it lacks the chronic features seen in lichen planus, discussed below.

lacks the chronic features seen in lichen planus, discussed below.

### **Morphology**

Early lesions show a superficial perivascular, lymphocytic infiltrate associated with dermal edema and margination of lymphocytes along the dermoepidermal junction in intimate association with degenerating keratinocytes (Fig. 22-2B). With time, discrete, confluent zones of basal epidermal necrosis occur, with concomitant blister formation. In the more rare and severe form of this disease, toxic epidermal necrosis, the necrosis extends through the full thickness of the epidermis.

### *Clinical Features*

Erythema multiforme manifests with a broad range of severity. The forms associated with infection, most often herpesvirus, are sometimes termed erythema multiforme minor because of their less severe clinical presentation. More severe forms of this disease are termed erythema multiforme major, Stevens-Johnson syndrome, and toxic epidermal necrolysis. These latter clinical forms of this disease continuum can be life-threatening because they can cause sloughing of large portions of the epidermis and loss of moisture and infectious barriers. They are most often seen as idiopathic reactions to drugs such as antibiotics or nonsteroidal anti-inflammatory agents.





## CHRONIC INFLAMMATORY DERMATOSES

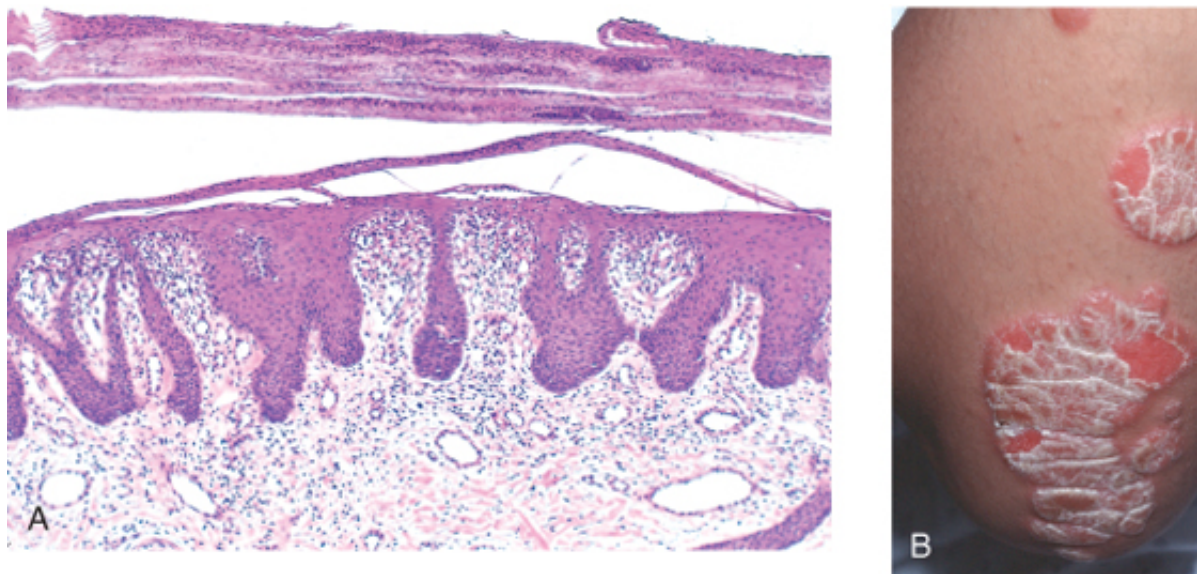
This category focuses on the persistent inflammatory dermatoses that exhibit their most character although they may begin with an acute stage. The skin surface in some chronic inflammatory derm excessive or abnormal scale formation and shedding (desquamation).

### Psoriasis

Psoriasis is a common chronic inflammatory dermatosis affecting 1% to 2% of people in the Unite with arthritis, myopathy, enteropathy, and spondylitic heart disease.

#### Pathogenesis

Psoriasis is an immunologic disease with contributions from genetic susceptibility and environmer antigens are self or environmental. Sensitized populations of T cells enter the skin, including derr accumulate in the epidermis. T cells homing to the skin secrete cytokines and growth factors that resulting in the characteristic lesions. Psoriatic lesions can be induced in susceptible individuals b *Koebner phenomenon*. The trauma may induce a local inflammatory response that promotes lesic severe psoriatic arthritis, recent therapeutics exploit advances in our understanding of T-cell biolo (1) T-cell activation and proliferation; (2) T cell trafficking and keratinocyte interaction with T cells; to its receptor thus inhibiting T cell functions.



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Figure 22-3 Psoriasis. **A**, Established plaques show marked epidermal hyperplasia with uniform downward exten: well as prominent parakeratotic scale focally infiltrated by neutrophils. Superficial fungal infections can show a strik should be excluded using special stains. **B**, Chronic plaques of psoriasis show silvery-white scale on ti

#### Morphology

There is marked epidermal thickening (**acanthosis**), with regular downward elonga (Fig. 22-3A). This downward growth has been likened to "test tubes in a rack." Incr turnover and lack of maturation results in **loss of the stratum granulosum with e parakeratotic scale**. There is thinning of the epidermal cell layer overlying the tips (suprapapillary plates) and blood vessels within the papillae are dilated and tortuou readily when the scale is removed, giving rise to multiple punctate bleeding points.



readily when the scale is removed, giving rise to multiple punctate bleeding points. Neutrophils form small aggregates within both the spongiotic superficial epidermis and the parakeratotic stratum corneum (**Munro microabscesses**). Similar changes can occur in fungal infections, and it is important to exclude this possibility with special stains in psoriasis.

### Clinical Features

Psoriasis most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal cleft. A *typical lesion is a well-demarcated, pink to salmon-colored plaque covered by loosely adherent silvery scales*. Nail changes occur in 30% of cases of psoriasis and consist of yellow-brown discoloration, with pitting and separation of the nail plate from the underlying bed (onycholysis). In most cases, psoriasis is limited to the skin, but it can be widespread and severe on occasion. There are a variety of clinical subtypes of this disease, defined by the pattern of involvement.

### Lichen Planus

"Pruritic, purple, polygonal, planar papules, and plaques" are the tongue-twisting traditional "*p's*" of lichen planus. Lichen planus is self-limited and usually resolves spontaneously 1 to 2 years after onset. Oral lesions are common.

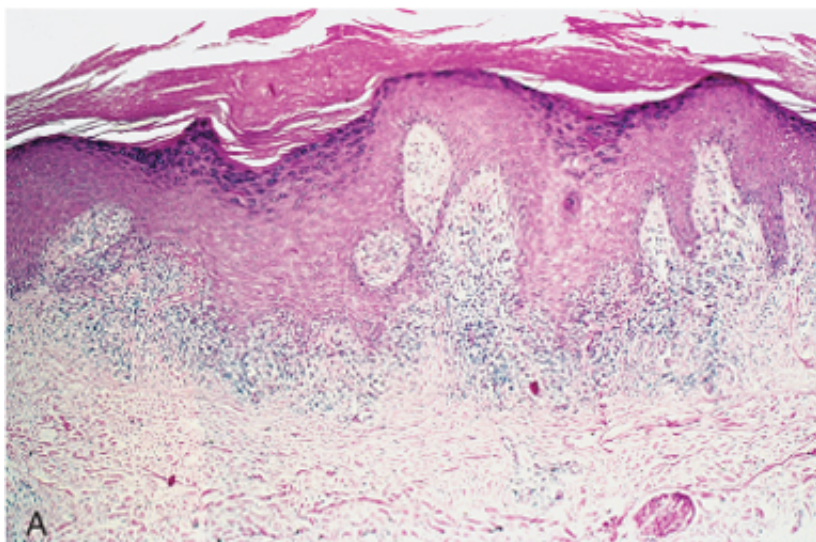
### Pathogenesis

The pathogenesis is not known. Expression of altered antigens at the level of the basal cell layer is thought to elicit a CD8+ T-cell-mediated cytotoxic immune response. The altered antigens could be due to viral infection or drug reaction.

### Morphology

Lichen planus, the prototypic **interface dermatitis**, is characterized by a dense, band-like infiltrate of lymphocytes along the dermoepidermal junction (Fig. 22-4A). The lymphocytes are in direct contact with basal keratinocytes that show degeneration and necrosis. Thus the changes are at the interface between the squamous epithelium and papillary dermis. Perhaps as a response to damage, the epidermis shows a resemblance in size and contour to more mature cells of the stratum spinosum (squamous atypia). The inflammation causes the dermoepidermal interface to assume an angulated, zigzag contour ("sawtoothing"). Anucleate, necrotic basal cells are seen in the inflamed papillary dermis as colloid bodies or **Civatte bodies**. Although these changes bear some similarities to those seen in lichenoid drug eruptions and lichenoid dermatitis multiforme (discussed earlier), lichen planus shows well-developed changes of hyperplasia, hypergranulosis, and hyperkeratosis.

### Clinical Features







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 Figure 22-4 Lichen planus. **A**, There is a band of lymphocytes along the dermoepidermal junction, and the rete architecture. This is also an interface dermatitis, but the infiltrate is more bandlike (lichenoid) than is seen in e hypergranulosis are definite signs of chronicity. **B**, Multiple flat-topped papules with white, lacey or netlike m

Cutaneous lesions consist of *pruritic, violaceous, flat-topped papules, which may coalesce focally* papules are often highlighted by white dots or lines, called *Wickham's striae*. Hyperpigmentation r dermis from the damaged basal cell layer. Multiple lesions are symmetrically distributed, particula wrists and elbows, and on the glans penis. In 70% of cases, oral lesions are present as white, reti mucosa.

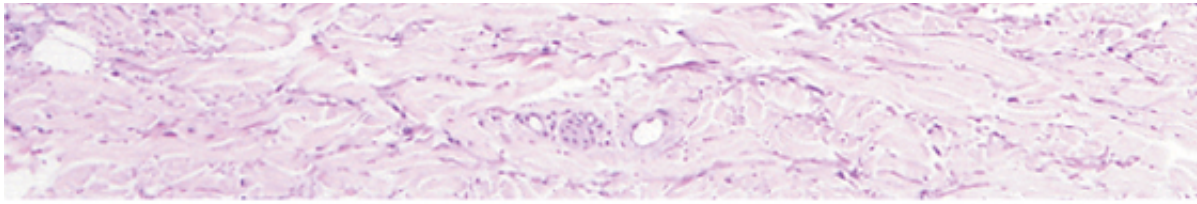
### Lichen Simplex Chronicus

Lichen simplex chronicus presents as roughening of the skin that takes on an appearance reminis to local repetitive trauma such as continual rubbing or scratching. When this condition is localized

#### Pathogenesis

The pathogenesis of lichen simplex chronicus is not understood, but it is probable that repetitive tr eventual dermal scarring.





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 Figure 22-5 Lichen simplex chronicus. Acanthosis with hyperkeratosis and hypergranulosis are distinctive. Superficial inflammation is common. There is no overt cytologic atypia thus distinguishing this from squamous

### Morphology

Lichen simplex chronicus is characterized by **acanthosis** with **hyperkeratosis** and **hypergranulosis** and elongation of the rete ridges and fibrosis of the papillary dermis with a chronic inflammatory infiltrate (Figure 22-5). Interestingly, these lesions are similar to normal volar (palms and soles) skin by constant "trauma," but at these sites the changes appear to represent an adaptive response to stimuli.

### Clinical Features

The lesions are often raised and erythematous, with increased scale and can be mistaken for keratinocarcinoma. Lichen simplex chronicus is superimposed upon, and masks another (often pruritic) dermatosis. It is therefore important to identify the underlying cause, but keep in mind that the lesion can be entirely self-inflicted.

### SUMMARY

**Inflammatory Dermatoses** There are many specific inflammatory dermatoses caused by IgE antibodies (urticaria), antigen-specific T cells (eczema, erythema multiforme, and trauma (lichen simplex chronicus). The histologic features can be grouped into patterns of inflammation such as interface dermatitis (e.g. lichen planus and erythema multiforme), perivascular dermatitis, and panniculitis (inflammation in subcutaneous fat). Understanding the mechanism and the ability to organize the diseases into pathogenic categories is needed to diagnose specific skin diseases, since the features are often overlapping.







## INFECTIOUS DERMATOSES

### Bacterial Infection

Numerous bacterial infections occur in skin. These range from superficial infections caused by *Staphylococcus aureus* known as *impetigo*, to deeper dermal abscesses caused by anaerobes like *Pseudomonas aeruginosa*. The pathogenesis is similar to that of similar microbial infections elsewhere ([Chapter 19](#)).

#### Morphology

Skin biopsy typically shows spongiotic epidermis with a neutrophilic infiltrate. Bacteria can be demonstrated using Gram stain in the superficial epidermis. Microbiologic culture and testing for sensitivities to various antibiotics can be useful.

#### Clinical Features

One of the most common skin bacterial infections is *impetigo*; it is primarily seen in children but can also occur in adults. It involves direct contact, usually with *Staphylococcus aureus*, or less commonly *Streptococcus pyogenes*. It begins as a single small macule that rapidly evolves into a larger lesion with a "honey-colored crust" (dried serum). Common sites involved are the extremities, nose, and mouth ([Fig. 22-6](#)). Individuals colonized by *S. aureus* or *S. pyogenes* are more likely to suffer from this disease. A less common bullous form of impetigo that can mimic an allergic reaction can occur in children.

### Fungal Infection





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Figure 22-6 Microbial infections. This child's arm is involved by impetigo resulting from a superficial bacterial infection (New York.)

Fungal infections are varied and range from superficial infections with *Candida* species to life-threatening individuals with *Aspergillus* species. In general, a fungal infection can be very superficial (stratum corneum, the dermis or subcutis), or systemic involving skin by hematogenous spread (often in an immunocompromised host).

### Pathogenesis

Superficial infections are often associated with a neutrophilic infiltrate in the epidermis. While dermal neutrophil-rich abscesses, dermal fungal infections often elicit a granulomatous response, perhaps the immune system are driving the responses. The deeper infections are usually more destructive; in angioinvasive.

### Morphology

Superficial *Candida* infections often induce a clinical response that can mimic psoriasis. Superficial fungal infection, such infections can mimic psoriasis so closely that it is difficult to exclude infection in a new diagnosis of psoriasis. This indicates that there is a generalized response of skin to stimulation by the immune system. Deeper fungal infections cause greater tissue damage, probably induced by both the microbes themselves and the host response to their presence.

### Clinical Features

Superficial infections such as those seen with *Candida* usually show erythematous macules with satellite lesions. Deeper infections such as those seen with *Aspergillus* species in immunocompromised hosts are sometimes show evidence of local hemorrhage.

### Verrucae (Warts)

Verrucae are common lesions of children and adolescents, although they may be encountered at any age. They are caused by papillomavirus (HPV). Transmission usually involves direct contact between individuals or autoinoculation. They are usually limited, most often regressing spontaneously within 6 months to 2 years.

### Pathogenesis

As mentioned earlier, verrucae are caused by HPV. Some members of the HPV family are associated with cancers of the anogenital region (Chapters 18 and 19). However, in contrast to HPV-associated cancers, verrucae are caused by distinct low-risk HPV types that lack potential for causing malignant transformation. Mechanistically, HPV allows increased proliferation of epithelial cells and production of new virus. Normal immune response usually clears the tumors, but immunodeficiency can be associated with increased numbers and size of verrucae.

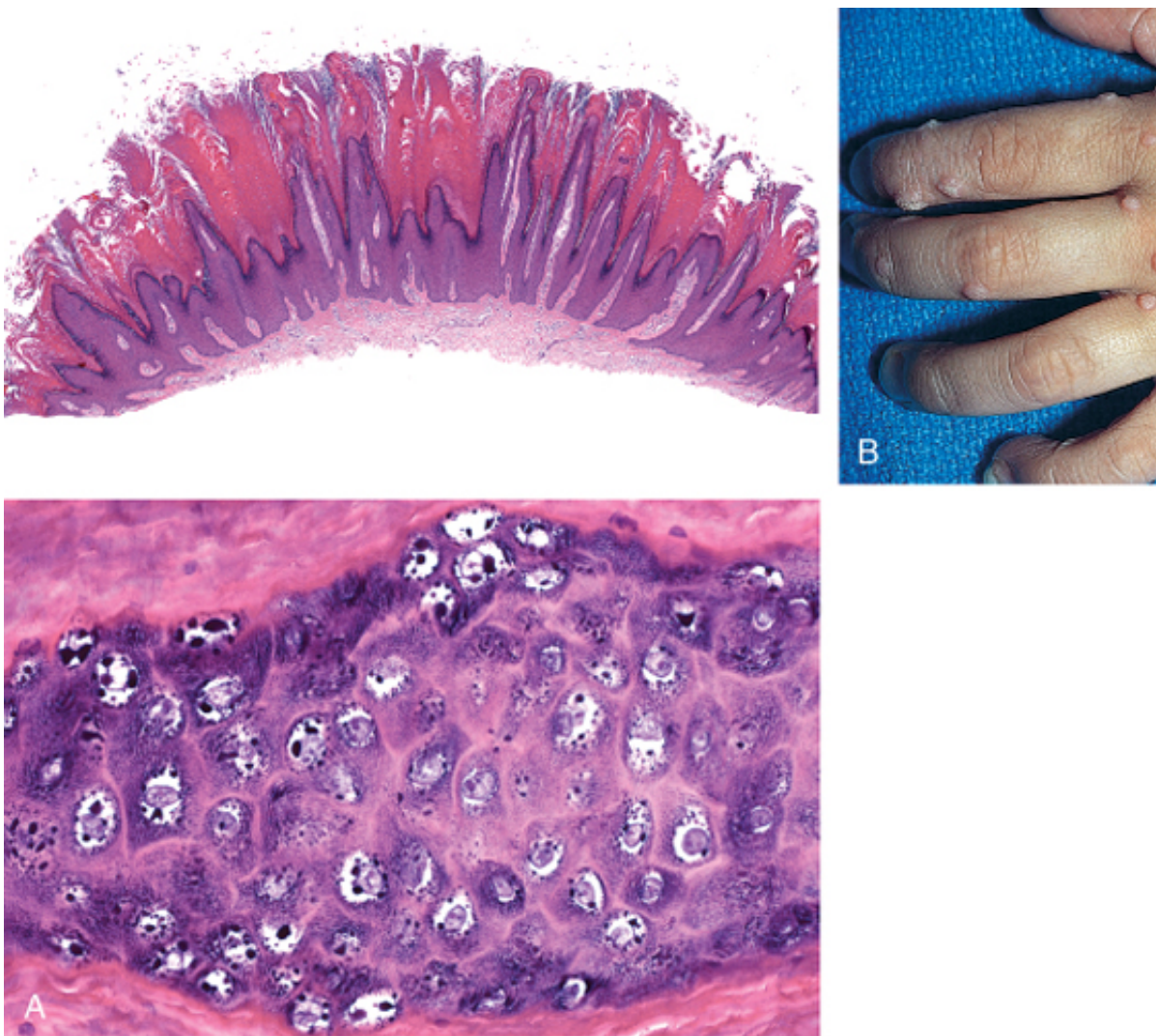
### Morphology

Histologic features common to verrucae include **epidermal hyperplasia** that is often papillomatous (so-called verrucous or papillomatous epidermal hyperplasia; Fig. 22-7A, top) and **(koilocytosis)** that preferentially involves the more superficial epidermal layers, particularly the stratum corneum, surrounding infected nuclei. Infected cells may also demonstrate prominent keratinization and jagged eosinophilic intracytoplasmic protein aggregates as a result of impaired maturation (Fig. 22-7A, bottom).

### Clinical Features







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 Figure 22-7 Verruca vulgaris. **A**, Lesions are formed by symmetric zones of papillary epidermal proliferation that crown (top). Nuclear pallor, prominent keratohyalin granules, and related cytopathic changes of human papillor (bottom). **B**, Multiple papules with rough, pebble-like surfaces at infection

Warts can be classified into several types on the basis of their morphology and location. In addition, they are caused by a distinct HPV type. *Verruca vulgaris* is the most common type of wart. These lesions occur on the hands, particularly on the dorsal surfaces and periungual areas, where they appear as gray-white papules with a rough, pebble-like surface (Fig. 22-7B). *Verruca plana*, or flat wart, is common on the face. These warts are flat, smooth, tan macules. *Verruca plantaris* and *verruca palmaris* occur on the soles of the feet. These rough, scaly lesions may reach 1 to 2 cm in diameter, coalesce, and be confused with ordinary carcinoma (wart) occurs on the penis, female genitalia, urethra, and perianal areas (Chapters 18 and 19).

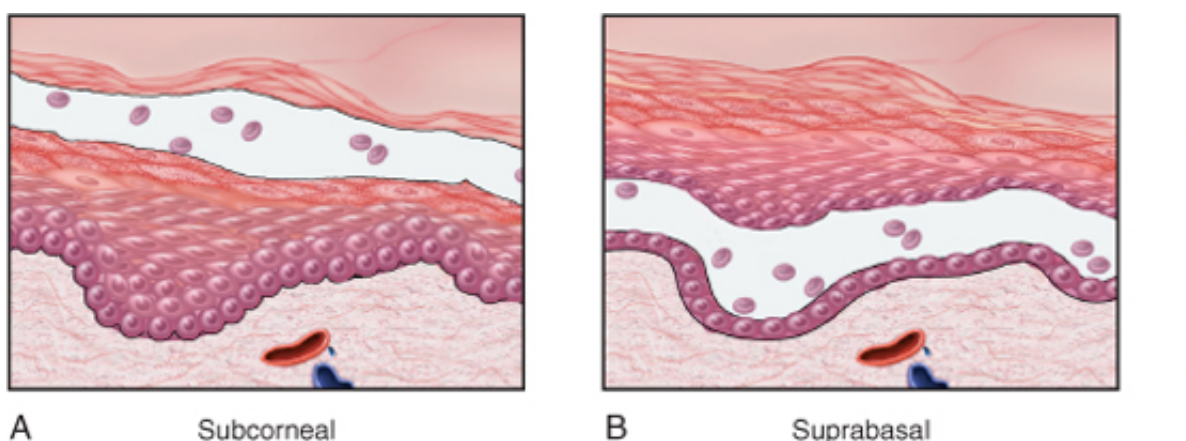




## BLISTERING (BULLOUS) DISORDERS

Although vesicles and bullae (blisters) occur as a secondary phenomenon in several unrelated conditions (e.g., spongiotic dermatitis), there is a group of disorders in which blisters are the primary and most distinctive feature. The level of blister formation within the skin, and assessment of their location within the skin is essential for an accurate diagnosis.

### Pemphigus (Vulgaris and Foliaceus)



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Figure 22-8 Levels of blister formation. **A**, Subcorneal (as in pemphigus foliaceus). **B**, Suprabasal (as in pemphigus vulgaris or dermatitis herpetiformis). Assessment of the levels of epidermal separation forms the basis of the classification of these disorders.

Pemphigus is a rare autoimmune blistering disorder resulting from loss of integrity of normal intercellular adhesion between keratinocytes of the epidermis and mucosal epithelium. Most individuals who develop pemphigus are middle-aged and older. The three main types are (1) pemphigus vulgaris, (2) pemphigus foliaceus, and (3) paraneoplastic pemphigus. The latter is associated with internal malignancy and will not be discussed here.

#### Pathogenesis

Both pemphigus vulgaris and pemphigus foliaceus are caused by a type II hypersensitivity reaction to an unknown antigen; [Chapter 5](#)) and show linkage to specific HLA types. Patient sera contain pathogenic IgG antibodies that bind to desmoglein types 1 and 3 of skin and mucous membranes. The distribution of these proteins determines the location of the lesions. By direct immunofluorescence, lesional sites show a characteristic netlike pattern of IgG deposition ([Fig. 22-9](#)). The antibodies seem to function primarily by disrupting the intercellular adhesive function of keratinocytes, and intercellular proteases as well.

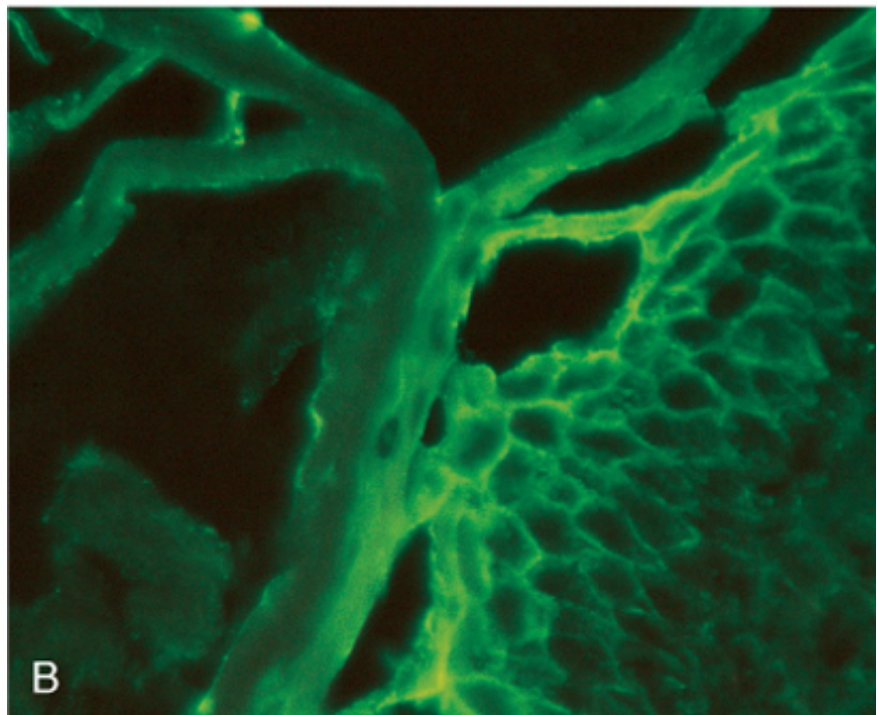
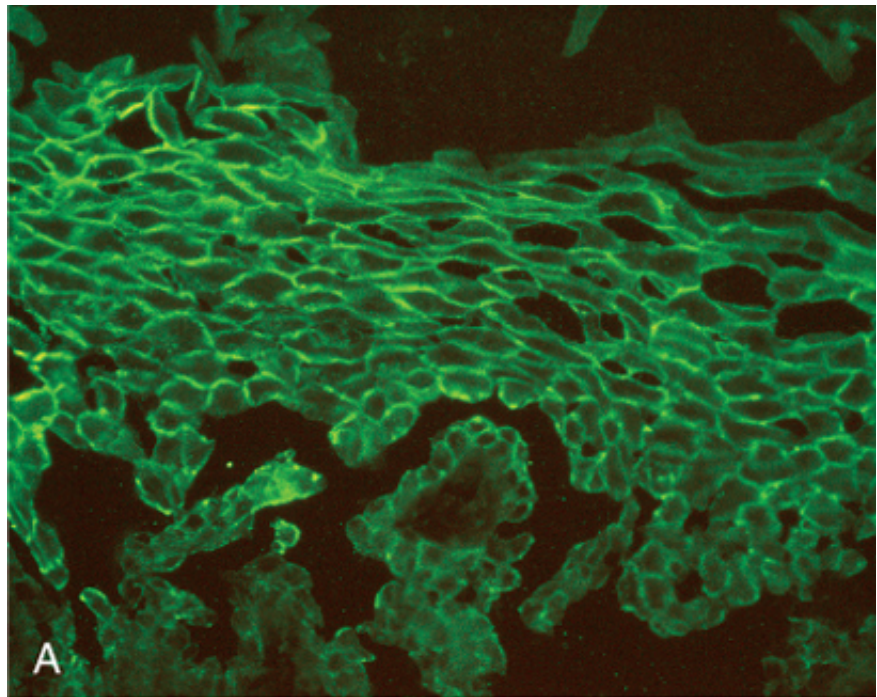
#### Morphology

The common histologic denominator in all forms of pemphigus is **acantholysis** (lysis of intercellular adhesion sites) within a squamous epithelial surface. Detached from their mooring sites, keratinocytes become rounded. In pemphigus vulgaris, acantholysis selectively involves the layer of the epidermis above the basal cell layer, giving rise to a **suprabasal acantholytic blister** ([Fig. 22-11B](#)). In pemphigus foliaceus, acantholysis selectively involves the superficial epidermis at the level of the stratum corneum ([Fig. 22-11A](#)). Variable superficial dermal infiltration by lymphocytes, histiocytes, and neutrophils accompanies all forms of pemphigus.

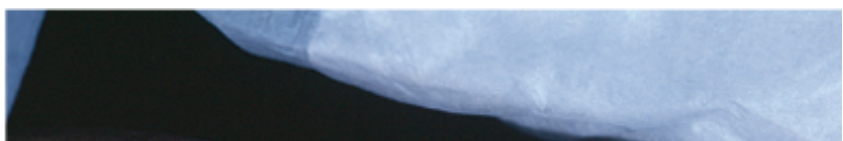
#### Clinical Features

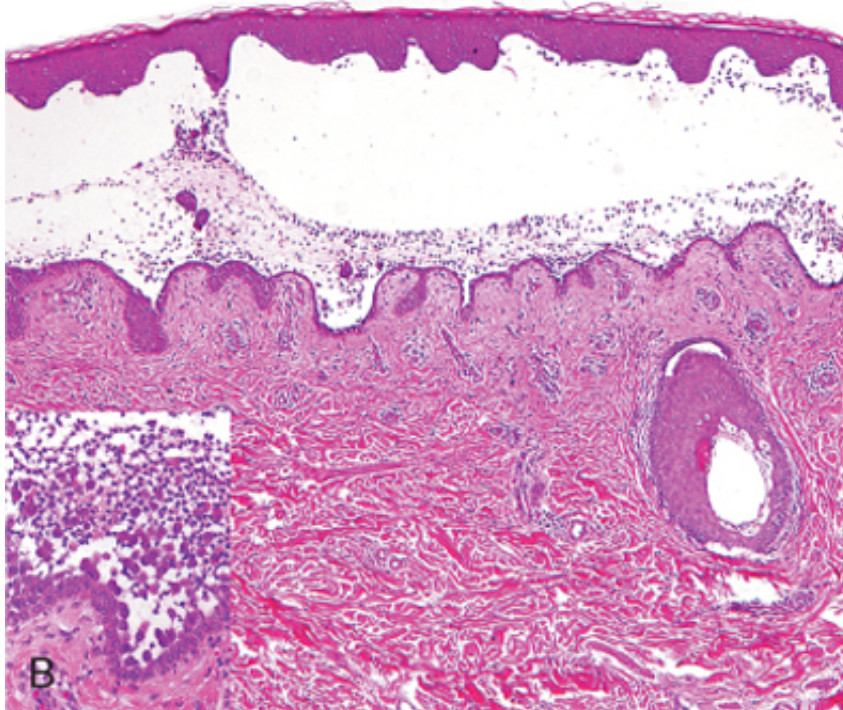






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 Figure 22-9 **A**, Pemphigus vulgaris. There is uniform deposition of immunoglobulin and complement (*green*) along the epidermal surface, characteristic "fishnet" appearance. **B**, The immunoglobulin deposits are more superficial





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Figure 22-10 Pemphigus vulgaris. **A**, This eroded area on the leg represents confluent blisters with loss of their roofs. **B**, This intraepidermal blister containing rounded keratinocytes that are separating from their neighbors. Initially, a single blister (suprabasal split), but these cells can divide and repopulate this area with keratinocytes, as seen in this case. Follicular involvement by acantholysis is also common.

*Pemphigus vulgaris*, by far the most common type, involves mucosa and skin, especially on the soles of the feet. The primary lesions are superficial vesicles and bullae that rupture easily, leaving erosions (Fig. 22-10A). *Pemphigus foliaceus*, a more rare and benign form of pemphigus, results in bullae confined to the mucous membranes. The blisters are so superficial that only zones of erythema and crusting sites are left (Fig. 22-11A). An epidemic form occurs in South America (*fogo selvagem*), putatively associated with consumption of a specific food.

### Bullous Pemphigoid

Generally affecting elderly individuals, bullous pemphigoid shows a wide range of clinical presentations. The primary lesions are large, tense bullae that rupture easily, leaving erosions.



cutaneous lesions and involvement of mucosal surfaces.

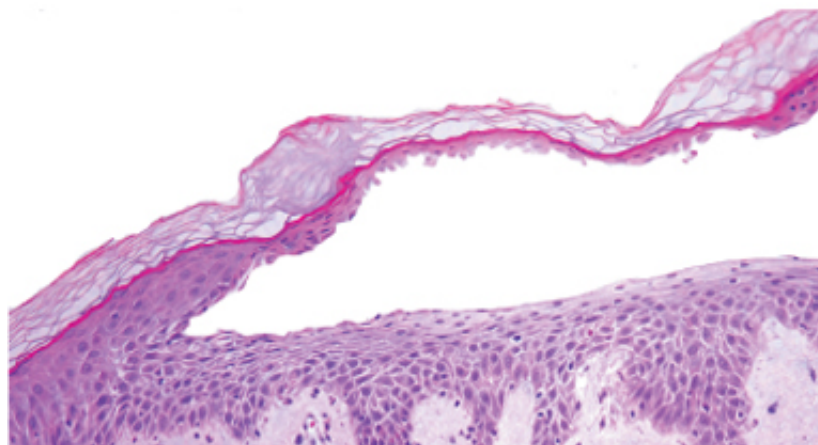
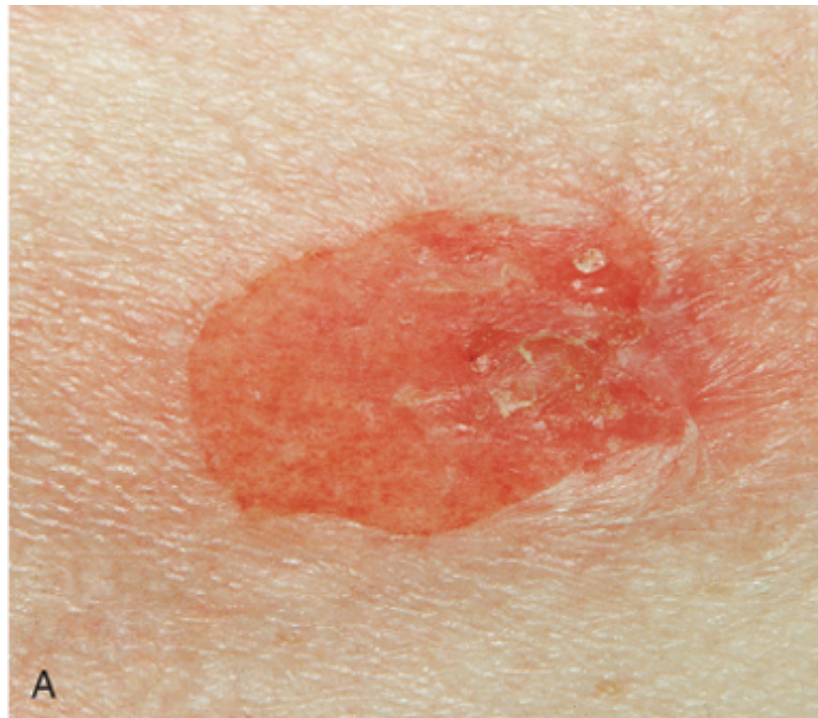
### *Pathogenesis*

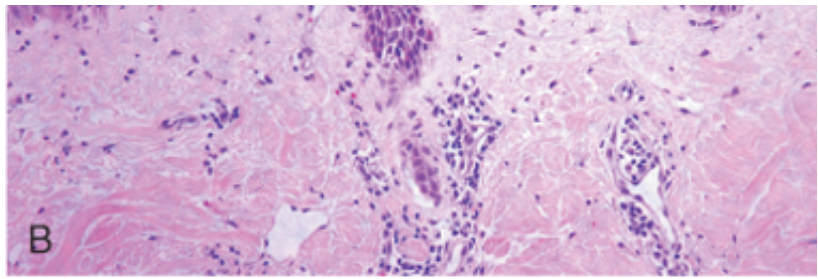
Bullous pemphigoid is an autoimmune disease in which the characteristic finding is linear deposits in the basement membrane zone (Fig. 22-12A). Reactivity also occurs in the basal cell-basement membrane junction (hemidesmosomes), where most of the bullous pemphigoid antigen (BPAG) is located. This protein is involved in cell-matrix bonding. IgG autoantibodies to hemidesmosome components fix complement with subsequent neutrophil and eosinophil infiltration.

### **Morphology**

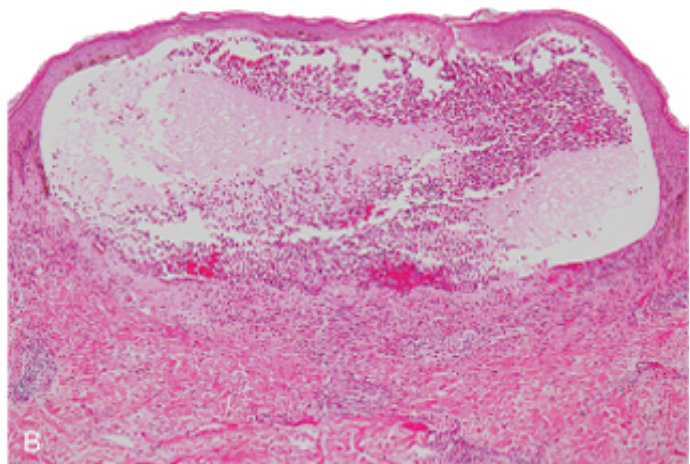
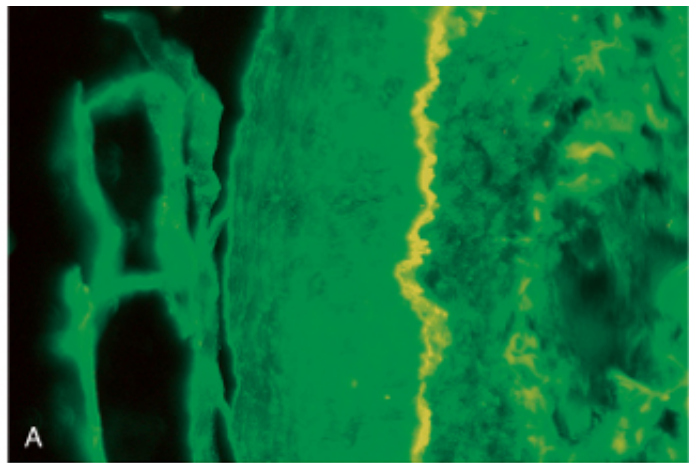
Bullous pemphigoid is characterized by a **subepidermal, nonacantholytic** blister. There is a perivascular infiltrate of lymphocytes and variable numbers of eosinophils, occasional dermal edema, and associated basal cell layer vacuolization. The vacuolated basal cells rise to a fluid-filled blister (Fig. 22-12B). Because the blister roof involves full-thickness epidermis, it is resistant to rupture unlike blisters in pemphigus.

### *Clinical Features*





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 Figure 22-11 Pemphigus foliaceus. **A**, Blisters are much less erosive than those seen in pemphigus vulgaris, situated just below the stratum corneum (subcorneal). **B**, Subcorneal separation of the epithelium is seen.





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Figure 22-12 Bullous pemphigoid. **A**, In bullous pemphigoid, both IgG antibody and complement can be detected outlining the subepidermal basement membrane zone (epidermis is on the left side of the fluorescent band). **B**, infiltrate rich in eosinophils. **C**, Tense, fluid-filled blisters result from vacuolization of the basal layer, producing subepidermal blisters (Prieto, Houston, Texas.)

Clinically, lesions are tense bullae, filled with clear fluid, on normal or erythematous skin (Fig. 22-12C) as in pemphigus and, if uncomplicated by infection, heal without scarring. Sites of occurrence include surfaces of the forearms, axillae, groin, and lower abdomen. Oral involvement is present in as many as 50% of patients. Bullous pemphigoid (also known as *herpes gestationis*, a misnomer, since there is no viral etiology) occurs during pregnancy and resolves after childbirth.

### Dermatitis Herpetiformis

Dermatitis herpetiformis is a rare disorder characterized by *urticaria and grouped vesicles*. The disease occurs in the third and fourth decades. In some cases it occurs in association with intestinal celiac disease (Chapter 15).

#### Pathogenesis

The association of dermatitis herpetiformis with celiac disease provides a clue to its pathogenesis. Patients with dermatitis herpetiformis develop IgA antibodies to dietary gluten (derived from the wheat protein gliadin). The antibodies cross-react with the anchoring fibrils that tether the epidermal basement membrane to the superficial dermis. The result is a subepidermal blister. Some people with dermatitis herpetiformis and gluten-sensitive enteropathy

#### Morphology

As an early event, fibrin and neutrophils accumulate selectively at the tips of dermal papillae, forming microabscesses (Fig. 22-13A). The basal cells overlying these microabscesses show ballooning degeneration and dermoepidermal separation that ultimately coalesce to form a true subepidermal blister. On immunofluorescence, dermatitis herpetiformis shows discontinuous, granular deposits of IgA localized in the tips of dermal papillae (Fig. 22-13B).

#### Clinical Features

The urticarial plaques and vesicles of dermatitis herpetiformis are extremely *pruritic*. The lesions are distributed symmetrically, involving preferentially the extensor surfaces, elbows, knees, upper back, and buttocks (Fig. 22-13C).

### SUMMARY

**Blistering Disorders** Blistering disorders are traditionally classified according to where the separation occurs. This group of diseases is often caused by auto-antibodies to constituents of the epithelium or basement membrane. Pemphigus is associated with auto-antibodies to intercellular desmogleins with resulting acantholysis that results in the formation of bullae that are subcorneal (superficial) in pemphigus foliaceus and superficial in pemphigus vulgaris. Bullous pemphigoid shows deposition of IgG auto-antibodies to basement membrane proteins and produces a subepidermal blister. Dermatitis herpetiformis shows deposition of IgA auto-antibodies to fibrils that bind epidermal basement membrane to the dermis, producing subepidermal blisters. This disease may be associated with celiac disease.



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## TUMORS

### Benign and Premalignant Epithelial Lesions

Benign epithelial neoplasms are common and usually biologically inconsequential. These tumors reside in the epidermis and hair follicles, that tend to differentiate toward cells and structures in the overwhelming majority of these tumors show limited growth and do not undergo malignant transfo

### Seborrheic Keratosis

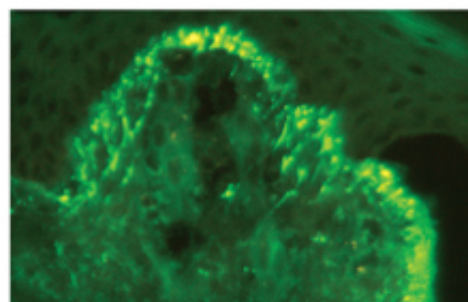
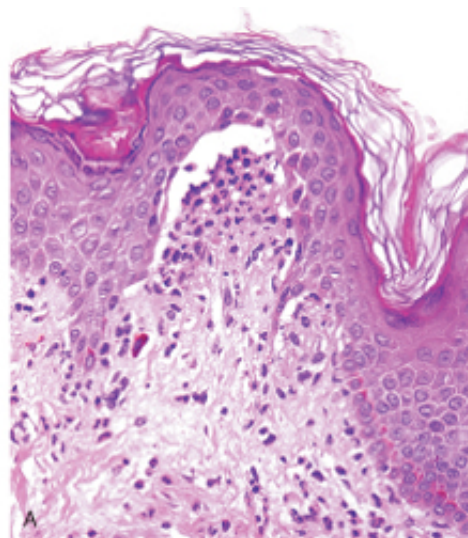
These common epidermal tumors occur most frequently in middle-aged or older individuals. They are particularly numerous on the trunk, although the extremities, head, and neck may also be involve

### Pathogenesis

Recent work has demonstrated that a significant fraction of these tumors harbor activating mutatio *receptor 3*. The explosive onset of hundreds of lesions may occur as a *paraneoplastic syndrome* ( Patients with this presentation may harbor internal malignancies that produce growth factors that :

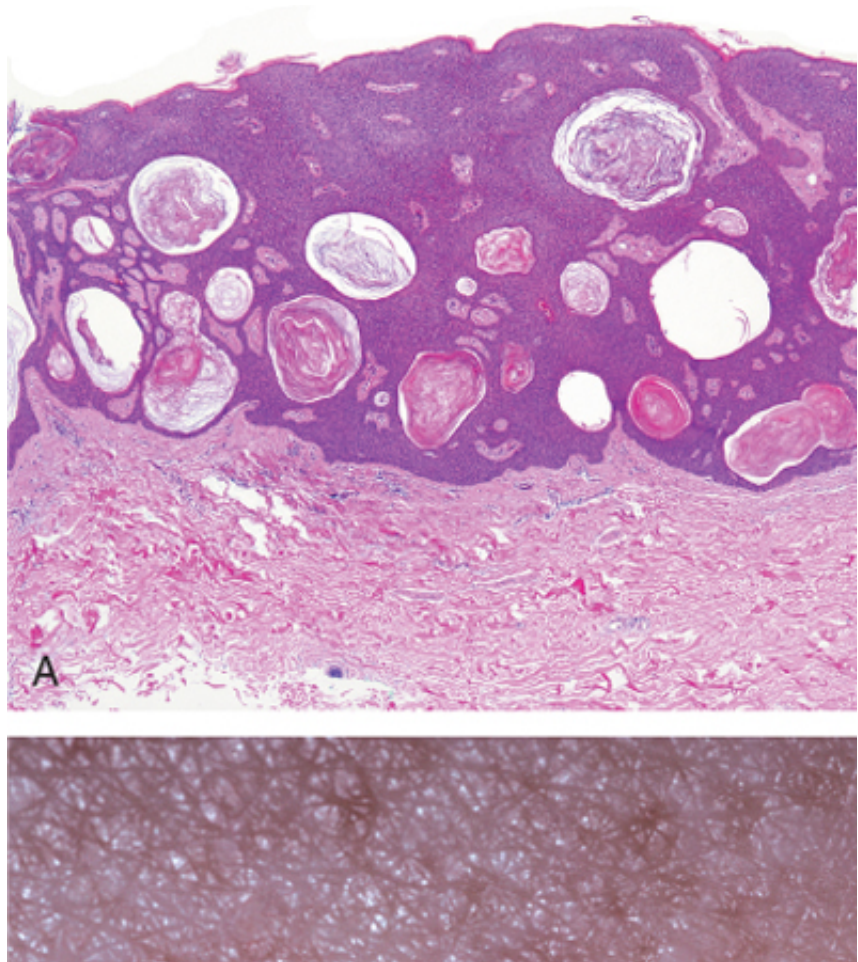
### Morphology

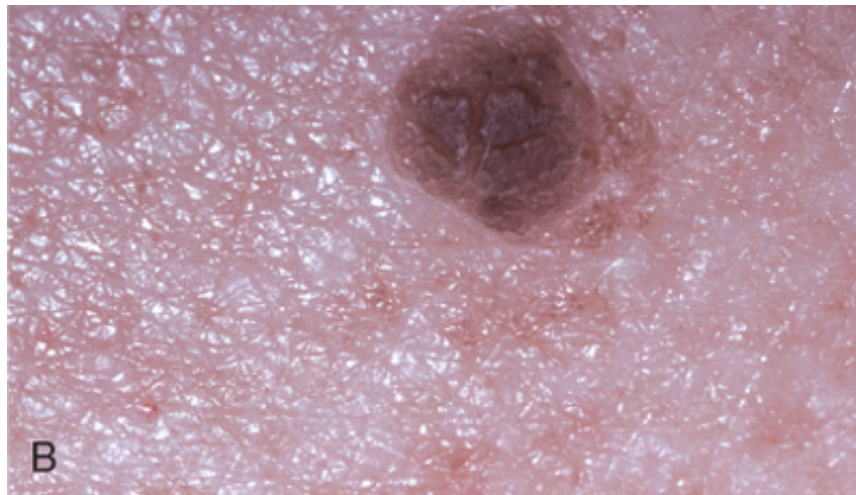
These neoplasms are exophytic and composed of sheets of small cells that most r basal cells of the normal epidermis ([Fig. 22-14A](#)). Variable melanin pigmentation is basaloid cells, accounting for the brown coloration seen clinically. Hyperkeratosis c the presence of small keratin-filled cysts (horn cysts) and down-growths of keratin (pseudo-horn cysts) are characteristic features.





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 Figure 22-13 Dermatitis herpetiformis. **A**, The blisters are associated with basal cell layer injury initially caused by the tips of dermal papillae. **B**, Selective deposition of IgA autoantibody at the tips of dermal papillae is characteristic (scratched) erythematous blisters, often grouped (seen here on elbows and arms). (**B**, Courtesy of Dr





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Figure 22-14 Seborrheic keratosis. **A**, The lesions consist of an orderly proliferation of uniform, benign basaloid microcysts (horn cysts). **B**, This roughened, brown, waxy lesion almost appears to be

#### *Clinical Features*

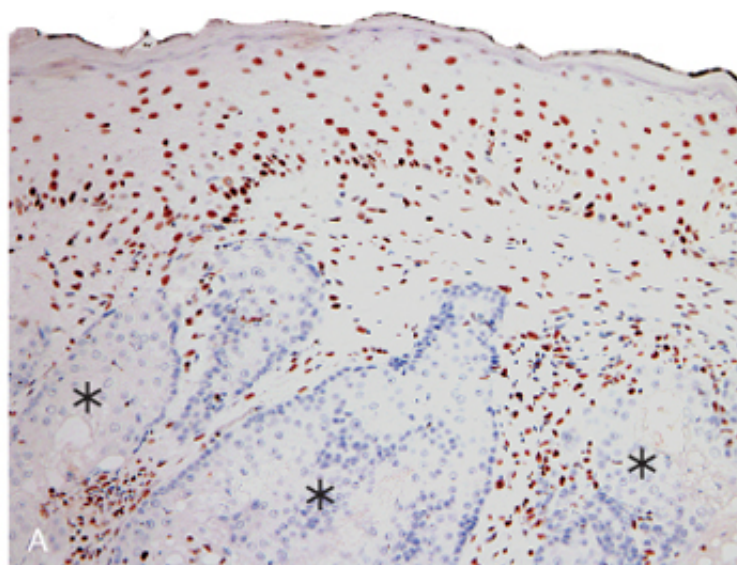
Clinically, seborrheic keratoses appear as *round, flat, coin-like plaques that vary in diameter from* They are tan to dark brown and usually show a velvety to granular surface. Occasionally, they bec because of their pigmentation, warranting their removal.

#### **Sebaseous Adenoma**

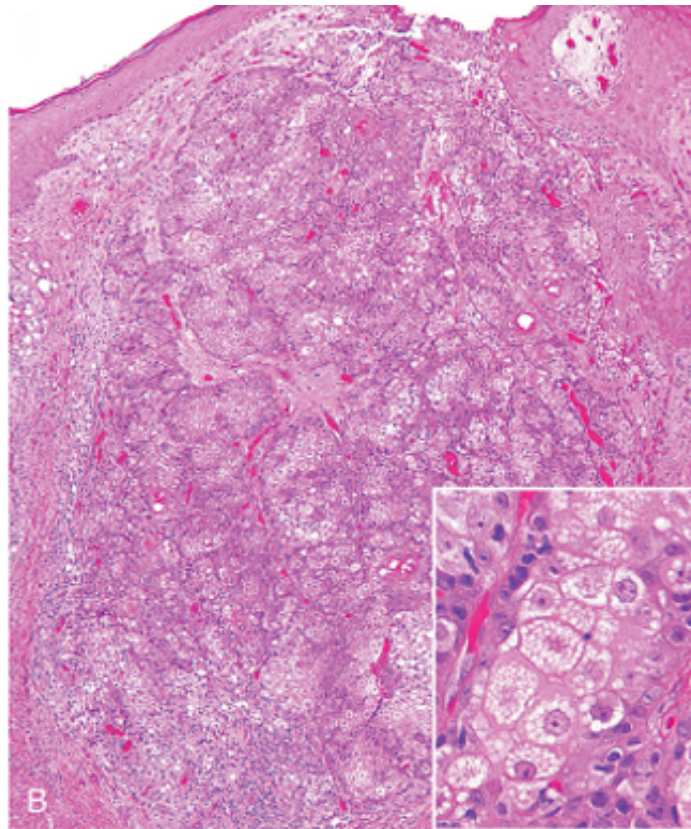
Sebaseous adenomas are rare tumors that primarily occur in the head and neck region of older in colored papules and can be a marker for an internal malignancy. Knowledge of this association ca

#### *Pathogenesis*

Much has been learned about the pathogenesis of these tumors by their association with the Muir tumors may be multiple or be distributed outside of the head and neck region. In addition there ma colon carcinoma. These cases are a subset of the hereditary nonpolyposis colorectal carcinoma s syndrome is associated with microsatellite instability due to loss of a DNA mismatch repair protein







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 Figure 22-15 Sebaceous adenoma. **A**, Immunohistochemistry reveals loss of nuclear expression of the DNA mismatch repair protein p53 in normal epidermis and lymphocytes, indicating probable association with the Muir-Torre syndrome. **B**, This lesion shows increased peripheral basaloid cells and more mature sebocytes in the central portion. Vacuolated cytoplasm is characteristic of mature sebocytes (inset, lower right corner).

### **Morphology**

Sebaceous adenomas show a lobular proliferation of sebocytes that maintain an orderly arrangement (Figure 22-15B). The basal cell layer is normally two cells thick, but this is variably expanded in the lesion. The lesion shows maturation to mature sebocytes in the center of the lesion. These cells have clear cytoplasm and are surrounded by vesicles filled with sebum. The tumors lack the severe cytologic atypia and infiltrative growth pattern of sebaceous carcinoma.

### **Clinical Features**

Sebaceous adenomas are benign, and their growth is usually self-limited. They tend to occur in areas where prominent sebaceous glands are normally present. Clinically these can be separated from the muir-torre syndrome, which has an umbilicated (dimpled) center and consists of hypertrophic sebaceous glands surrounded by a rim of basaloid cells.

### **Actinic Keratosis**

Before the development of overt malignancy of the epidermis, a series of progressively dysplastic changes in the epidermis, known as actinic keratosis, is usually the result of chronic exposure to sunlight and is associated with hyperkeratosis (thickening of the stratum corneum) and related keratoses.

### **Pathogenesis**

Whether all actinic keratoses would result in carcinoma with time is conjectural. Many lesions regress spontaneously, but some do become malignant to warrant local eradication. Mutation of *p53* is often an early event with most actinic keratoses and is related to light injury.

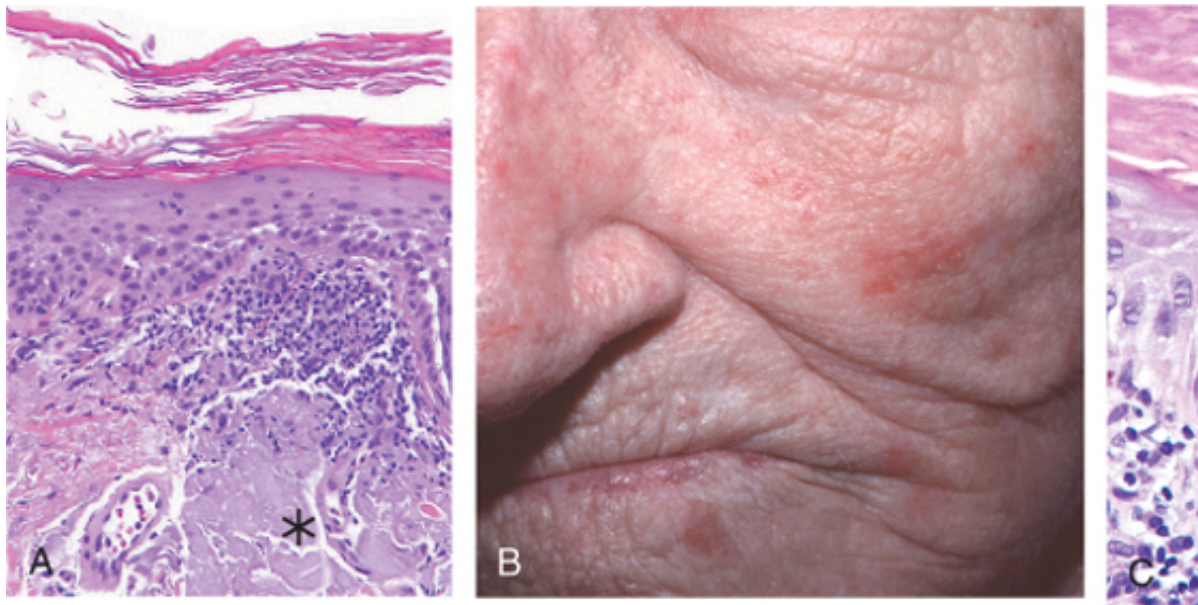


### Morphology

Lower portions of the epidermis show **cytologic atypia**, often with hyperplasia of basaloid nests with early atrophy that results in diffuse thinning of the epidermal surface of the lesion. Thickened, blue-gray elastic fibers (solar elastosis), the result of chronic sun damage, are often seen. The epidermis is thickened with retained nuclei (parakeratosis). Some but not all lesions progress to amounting to squamous cell carcinoma in situ (Fig. 22-16C). A useful acronym for histologic features is SPAIN—a sun-soaked country perfect for acquiring such lesions (sun damage), parakeratosis, atypia (keratinocytic), inflammation (lymphocytes in the dermis), and not full thickness (atypia). (Acronym courtesy of Dr. Zeina Tannous, Massachusetts General Hospital, Boston, Massachusetts.)

### Clinical Features

Lesions of actinic keratosis, very common in fair-skinned individuals, are usually *less than 1 cm in diameter, well-circumscribed, and have a rough, sandpaper-like consistency* (Fig. 22-16B). As would be expected, they occur on sun-exposed areas (face, arms, dorsum of the hands), and the lesions accumulate with age and degree of sun exposure. Lesions can be treated with cryotherapy (superficial freezing) or topical chemotherapeutic and other agents.



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Figure 22-16 Actinic keratosis. **A**, Basal cell layer atypia (dysplasia) is associated with marked hyperkeratosis, parakeratosis, and inflammation. **B**, Most lesions form subtle zones of redness or sandpaper-like keratinization as seen in the lesions on the cheek. **C**, Lesions show full-thickness atypia, qualifying as carcinoma in situ.

### SUMMARY

**Benign and Premalignant Tumors**  
**Seborrheic Keratosis:** Round, flat plaque with proliferating monotonous basal cells of epidermis containing melanin. Hyperkeratosis and cysts characteristic.  
**Sebacous Adenoma:** Multiple flesh-colored nodules arising from sebaceous glands. May be a marker of internal malignancy.  
**Actinic Keratosis:** Present on sun-exposed skin, the lower parts of epidermis, that can infrequently progress to carcinoma *in situ*.

### Malignant Epidermal Tumors

## **Squamous Cell Carcinoma**

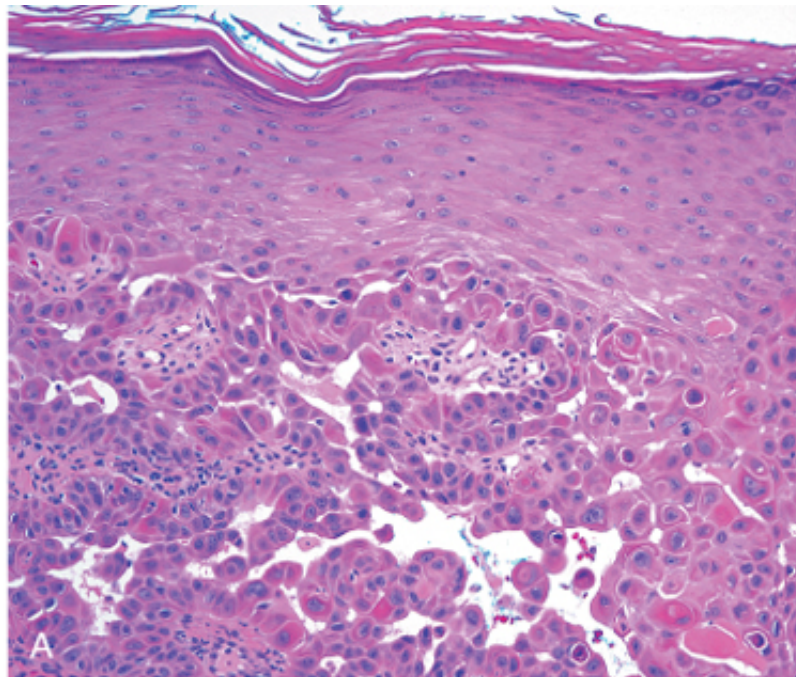
Squamous cell carcinoma is a *common tumor arising on sun-exposed sites in older people*. Except tumors have a higher incidence in men than in women. In addition to sunlight, predisposing factors (oils), chronic ulcers, old burn scars, ingestion of arsenicals, and ionizing radiation.

### **Pathogenesis**

The most common exogenous cause of cutaneous squamous cell carcinoma is UV light exposure damage (Chapter 6). Individuals who are immunosuppressed as a result of chemotherapy or organ transplantation, or xeroderma pigmentosum, are at increased risk. In addition to inducing mutations, UV light (UVB) has an immunosuppressive effect on skin by impairing antigen presentation by Langerhans cells. This may be weakening immunosurveillance. Immunosuppressed patients, particularly organ transplant recipients, are at high risk for HPV types. *p53* mutations with associated UV mutation signatures are common, as are active cell carcinomas at other sites, those in the skin may be preceded by *in situ* lesions.

### **Morphology**

Squamous cell carcinoma in situ is characterized by highly atypical cells at all levels of the epidermis, with nuclear crowding and disorganization. The squamous dysplasia is broad and occupies the entire epidermis. When these cells break through the basement membrane, the process is invasive (Figure 22-17A). Invasive squamous cell carcinomas exhibit variable differentiation, ranging from well-differentiated atypical squamous cells arranged in orderly lobules showing large zones of keratin formation to highly anaplastic, rounded cells with foci of necrosis and only abortive keratinization (dyskeratosis). While morphologic variation is wide, all squamous cell carcinomas show some degree of keratinization.





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 Figure 22-17 Invasive squamous cell carcinoma. **A**, The carcinoma invades the dermis as irregular projections of a is acantholytic (i.e., the squamous cells are poorly cohesive). **B**, A nodular and hyperkeratotic lesion occurring on prominent postauricular lymph node (arrow).

### *Clinical Features*

Squamous cell carcinomas *in situ* appear as sharply defined, red, scaling plaques; many arise from invasive lesions are nodular, show variable scale, and may ulcerate (Fig. 22-17B). The likelihood the lesion and degree of invasion into the subcutis. Tumors arising in the context of actinic keratosis fashion, while those arising in burn scars, ulcers, and skin not exposed to the sun tend to behave

Invasive squamous cell carcinomas of the skin are often discovered while small and resectable; less nodes at diagnosis. Mucosal squamous cell carcinomas (oral, pulmonary, esophageal, etc.) are g

### **Basal Cell Carcinoma**

Basal cell carcinoma, the most common human cancer, is a *slow-growing tumor that rarely metas* to chronic sun exposure and in lightly pigmented people. As with squamous cell carcinoma, the in with immunosuppression (though not as dramatically as that of squamous cell carcinoma) and in i repair.

### *Pathogenesis*

Basal cell carcinoma has been associated with dysregulation of the sonic hedgehog, or *PTCH*, pa gene with subsequent loss of heterozygosity in the numerous individual tumor foci cause the fami syndrome. Thus, *PTCH* functions as a classic tumor suppressor. Since the *PTCH* pathway is also subtle developmental anomalies are also noted in these individuals. Some component of the *PTC* majority of sporadic basal cell carcinomas; mutations in *p53* are also common.

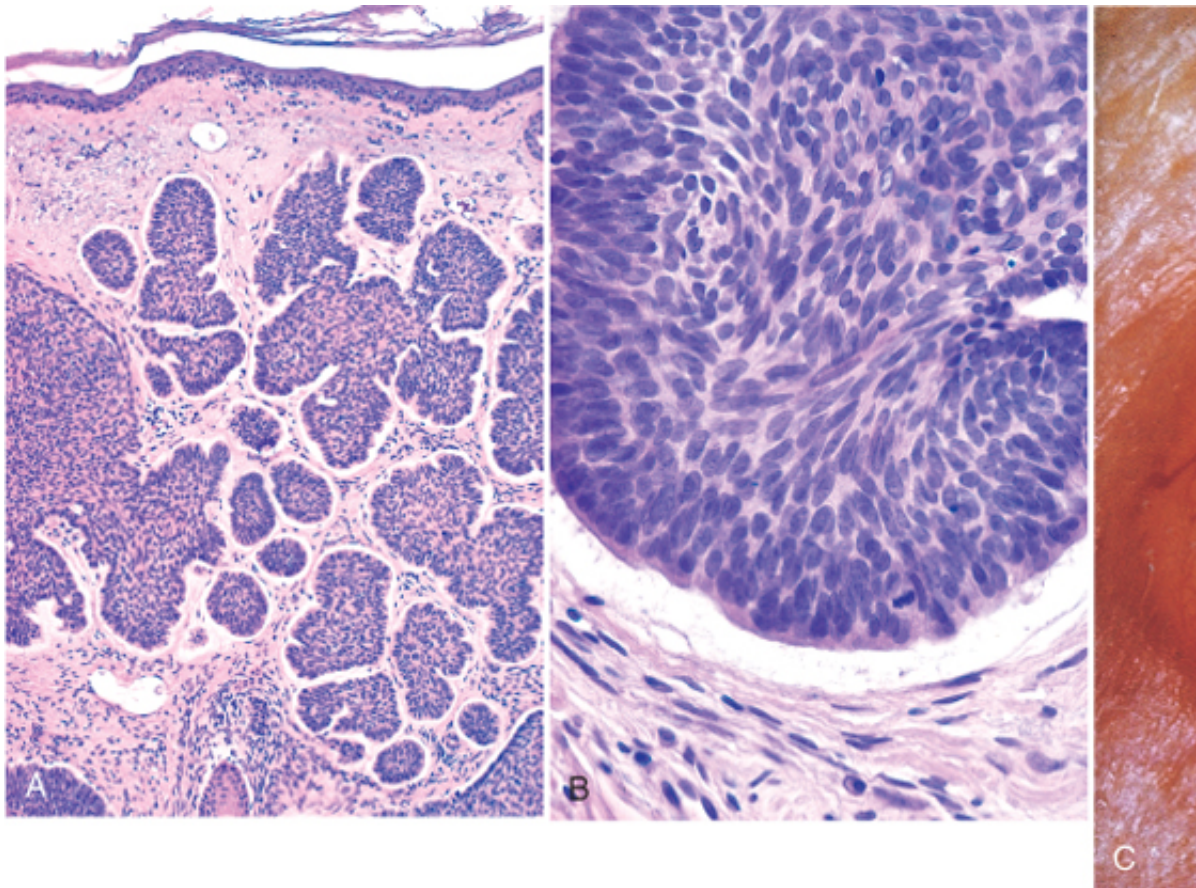
### **Morphology**

Tumor cells resemble the normal epidermal basal cell layer from which they are de from the epidermis or sometimes follicular epithelium, they are not encountered on common patterns are seen: either **multifocal growths** originating from the epiderm **nodular lesions** growing downward into the dermis as cords and islands of variab hyperchromatic nuclei, embedded in a fibrotic to mucinous matrix (Fig. 22-18A). Pe align in the outermost layer (palisading) with separation from the stroma, creating a (Fig. 22-18B).

### *Clinical Features*



Clinically, these tumors present as *pearly papules*, often containing prominent, dilated subepidermal (18C). Some tumors contain melanin pigment and thus appear similar to melanocytic nevi or melanomas. and extensive local invasion of bone or facial sinuses may occur after many years of neglect. The complete local excision, although immunomodulatory therapies that direct the innate immune response are being tested as well.



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Figure 22-18 Basal cell carcinoma. **A**, The lesion is formed by multiple nodules of basaloid cells infiltrating a fibrous stroma. Note the small hyperchromatic nuclei, and a peripheral palisade with clefting from the stroma. Note the similarity of these cells to those of a basaloid lesion. This lesion is a prototypical pearly, smooth-surfaced papule with associated telangiectases.

## SUMMARY

**Malignant Epidermal Tumors** The incidence of both basal cell and squamous cell carcinomas is strongly correlated with increasing lifetime sun exposure. Basal cell carcinoma, the most common malignant tumor world-wide, is a locally aggressive tumor associated with the basaloid pathway. Metastasis is exquisitely rare. Cutaneous squamous cell carcinoma arises from actinic keratoses but most arise from chemical exposure, at thermal burn sites, or HPV infection in the setting of immunosuppression. Cutaneous squamous cell carcinoma is capable of metastasis, but is much less aggressive than squamous cell carcinoma.

## Tumors and Tumor-Like Lesions of Melanocytes

### Melanocytic Nevi

Strictly speaking, the term *nevus* denotes any congenital lesion of the skin. *Melanocytic nevus*, however, denotes an acquired neoplasm of melanocytes.

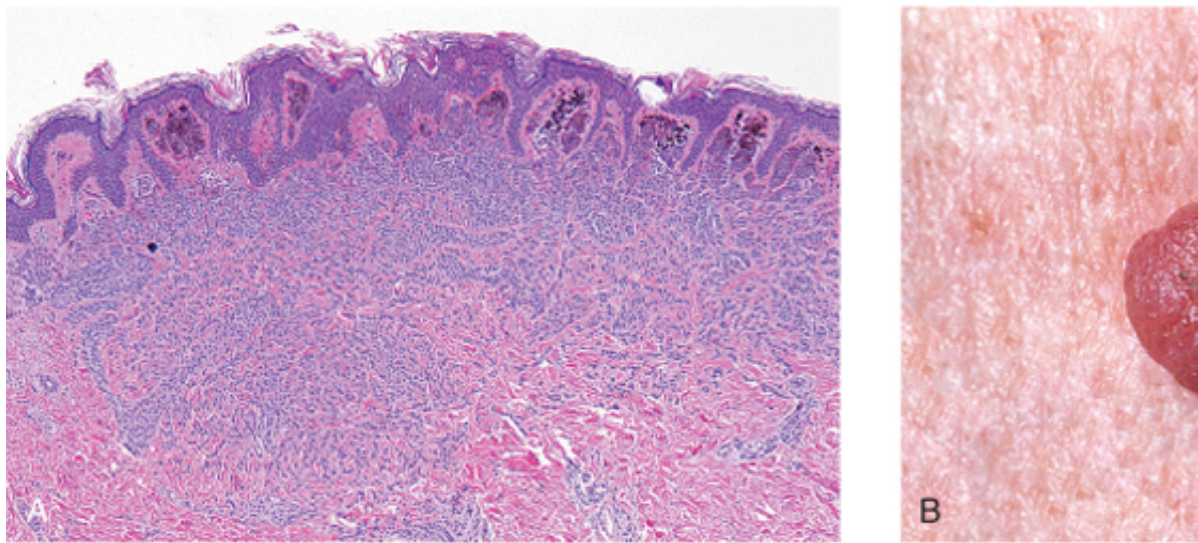


acquired neoplasm of melanocytes.

## Common Nevus

### Pathogenesis

Melanocytic nevi are derived from the transformation of highly dendritic melanocytes that are normally in the epidermis. Progressive growth of nevus cells from the dermoepidermal junction into the underlying dermis is called *maturation*. Superficial nevus cells are larger and less mature, tend to produce melanin pigment, and are more numerous. Deeper nevus cells are smaller and more mature, produce little or no pigment, and grow in cords. This sequence of maturation is of diagnostic importance, since melanomas usually show little or no maturation. The majority of benign melanocytic nevi have an activating mutation in BRAF (a protein downstream from RAS in the extracellular receptor kinase pathway). These two mutations are mutually exclusive; the growth of melanocytic nevi is self-limited.



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Figure 22-19 Melanocytic nevus. **A**, This dermal nevus shows rounded melanocytes extending into the dermis with maturation and more separated with depth—all reassuring signs of appropriate maturation. **B**, Melanocytic nevi are relatively common.

### Morphology

Melanocytic nevi are initially composed of round-to-oval cells that grow in "nests" at the dermoepidermal junction. Nuclei are uniform and round, and contain inconspicuous nucleoli with little cytoplasm. Such lesions, believed to represent an early developmental stage, are called **junctional nevi**. Most junctional nevi grow into the underlying dermis as nests or cords of cells (**compound nevi**). In older lesions the epidermal nests may be lost entirely to leave pure **dermal nevi** (Fig. 22-19B). Compound and dermal nevi are often more elevated than are junctional nevi.

### Clinical Features

Common melanocytic nevi are tan-to-brown, uniformly pigmented, small (usually  $\leq 5$  mm across), and have well-defined, rounded borders (Fig. 22-19B). There are numerous types of melanocytic nevi, usually these lesions are of cosmetic interest only (sometimes even referred to as "beauty spots" or "freckles"). On the face, they can become irritating or mimic melanoma and thus may be surgically removed.

### Dysplastic Nevus

Dysplastic nevi may occur *sporadically* or *in a familial form*. The latter are inherited in an autosomal dominant fashion and are precursors of melanoma. In the sporadic form, the risk of malignant transformation seems very low.

### Pathogenesis

A subset of dysplastic nevi are precursors of melanoma. In individuals with a family history of melanoma, the risk of malignant transformation is higher.

individuals who first develop dysplastic nevi. In these cases, the lifetime risk of developing melanoma is increased. The risk of developing melanoma from dysplastic nevi correlates with the risk of developing melanoma and transition from dysplastic nevi to melanoma is documented both clinically and histologically. Despite such documented evolution from dysplastic nevi to melanoma, most dysplastic nevi arise de novo and not from a preexisting nevus. Thus, the likelihood that any particular individual will develop into melanoma is exceedingly low. Consequently, these lesions should be viewed as markers of increased risk rather than as precursors. *BRAF* mutations are encountered in dysplastic as well as in melanocytic nevi; additional complex

### Morphology

Dysplastic nevi consist mainly of compound nevi with both architectural and cytologic atypia. In this sense they have some histologic and clinical properties that are reminiscent of melanoma. **Nevus cell nests within the epidermis may be enlarged and show fusion or coalescence with adjacent nests. As part of this process, single nests may replace the normal basal cell layer along the dermoepidermal junction, producing lentiginous hyperplasia** (see Fig. 22-22B). Cytologic atypia consisting of irregular nuclear contours and hyperchromasia is frequently observed (Fig. 22-20A, B). Associated with the superficial dermis. These consist of a sparse lymphocytic infiltrate, loss of melanin pigment, phagocytosis by dermal macrophages (melanin pigment incontinence), and linear and pagetoid intraepidermal nests of melanocytes. These are all elements of the host response to the

### Clinical Features

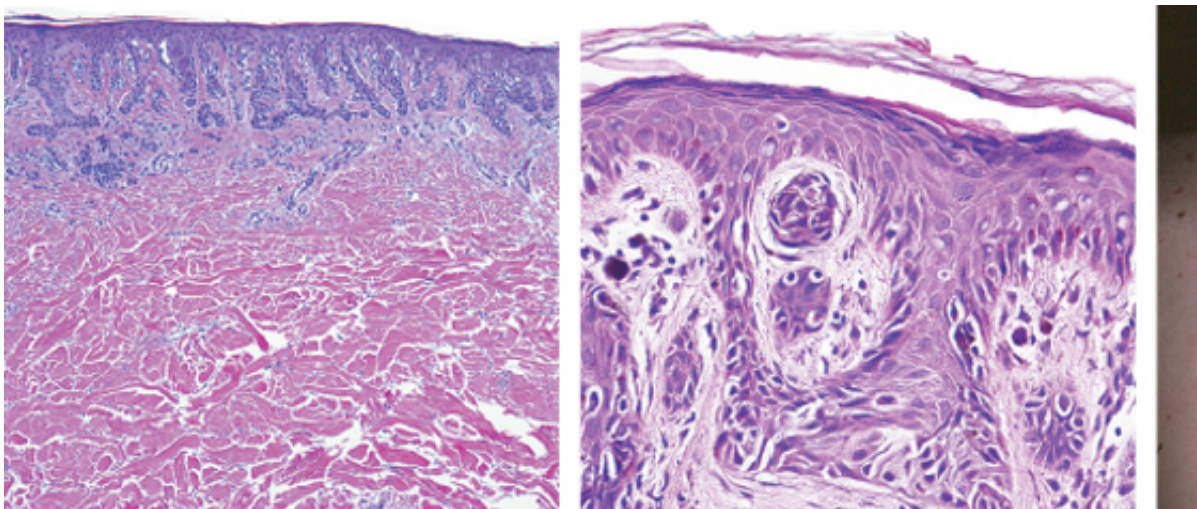
*Dysplastic nevi are usually larger than most acquired nevi* (often >5 mm across) and may occur anywhere on the body (Fig. 22-20C). They are flat macules to slightly raised plaques, with a "pebbly" surface. They usually have variegated pigmentation (variegation) and irregular borders (Fig. 22-20C, inset). Unlike ordinary nevi, *dysplastic nevi have been documented to occur on sun-exposed body surfaces*. Dysplastic nevi have been documented to be prone to the development of malignant melanoma (the "familial melanoma syndrome").

### Melanoma

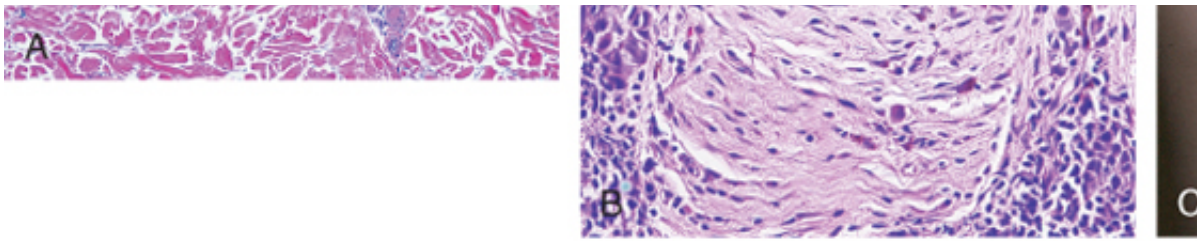
Melanoma is less common but much more deadly than basal or squamous cell carcinoma. Today, with increased awareness of the earliest signs of skin melanomas, most melanomas are cured surgically. Nonetheless, the incidence of melanoma has increased dramatically over the last several decades, at least in part a result of increasing sun exposure and surveillance.

### Pathogenesis

As with other cutaneous malignancies, sunlight plays an important role in the development of melanoma. Sunlight is a major risk factor for melanoma, particularly on sun-exposed skin and in geographic locales such as New Zealand and Australia where sun exposure is high. Intense intermittent exposure at an early age is particularly harmful. Sunlight, however, is not the only predisposing factor; the presence of preexisting nevi and hereditary predisposition also play a role

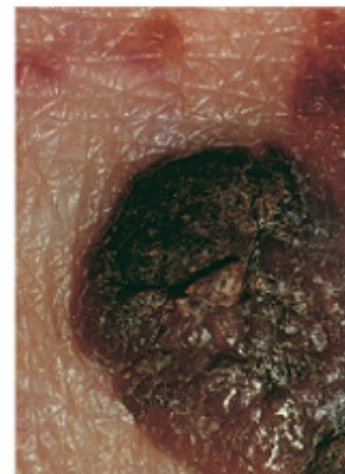
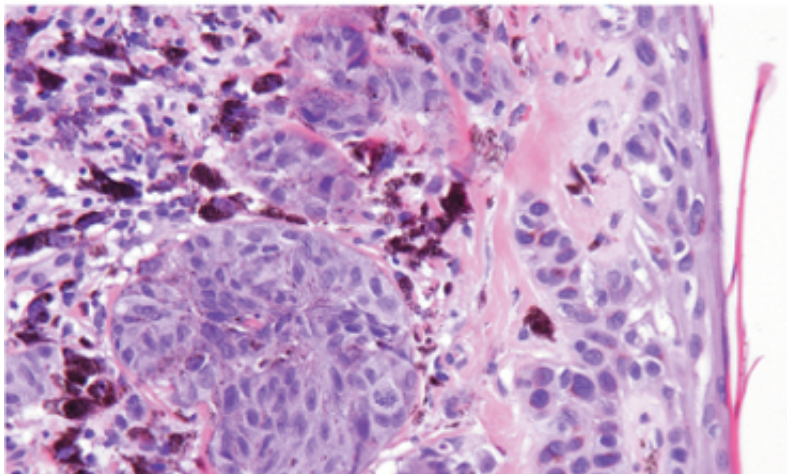
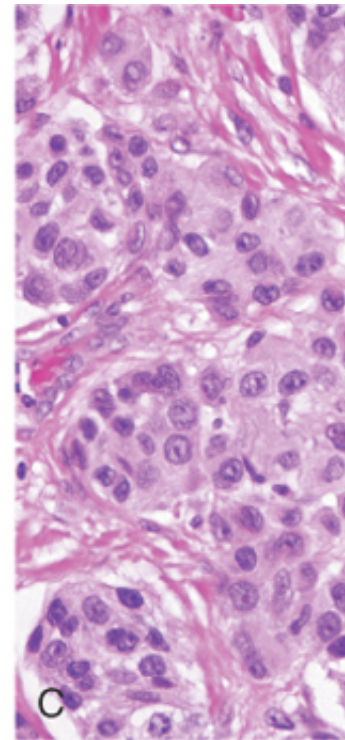
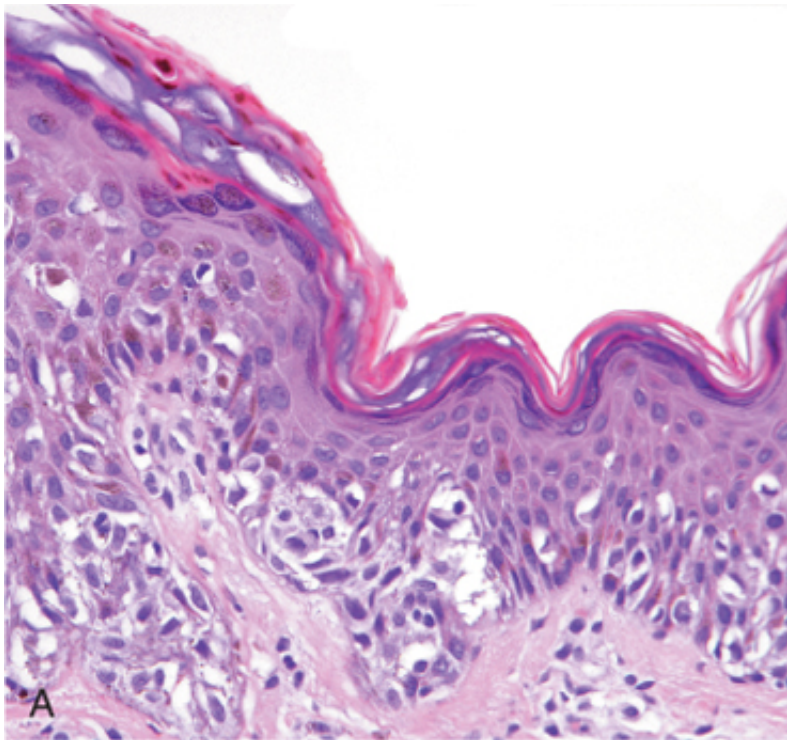


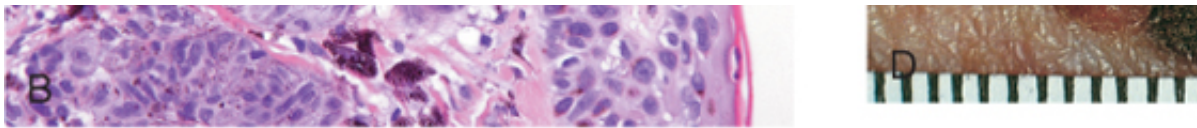




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Figure 22-20 Dysplastic nevus. **A**, Compound dysplastic nevi feature a central dermal component with an asymmetrical distribution of melanocytes (*left*). The former correlates with the more pigmented and raised central zone (see **C**, inset), and the **B**, An important feature is the presence of cytologic atypia (irregular, dark-staining nuclei) at high magnification. The bands of fibrosis often encountered in dysplastic nevi-part of the host response to these lesions. **C**, Numerous irregular melanocytes are present in the epidermis; the clinical features are intermediate to those of benign nevi and melanoma. The lesion is characterized by irregular borders and variable pigmentation (inset).

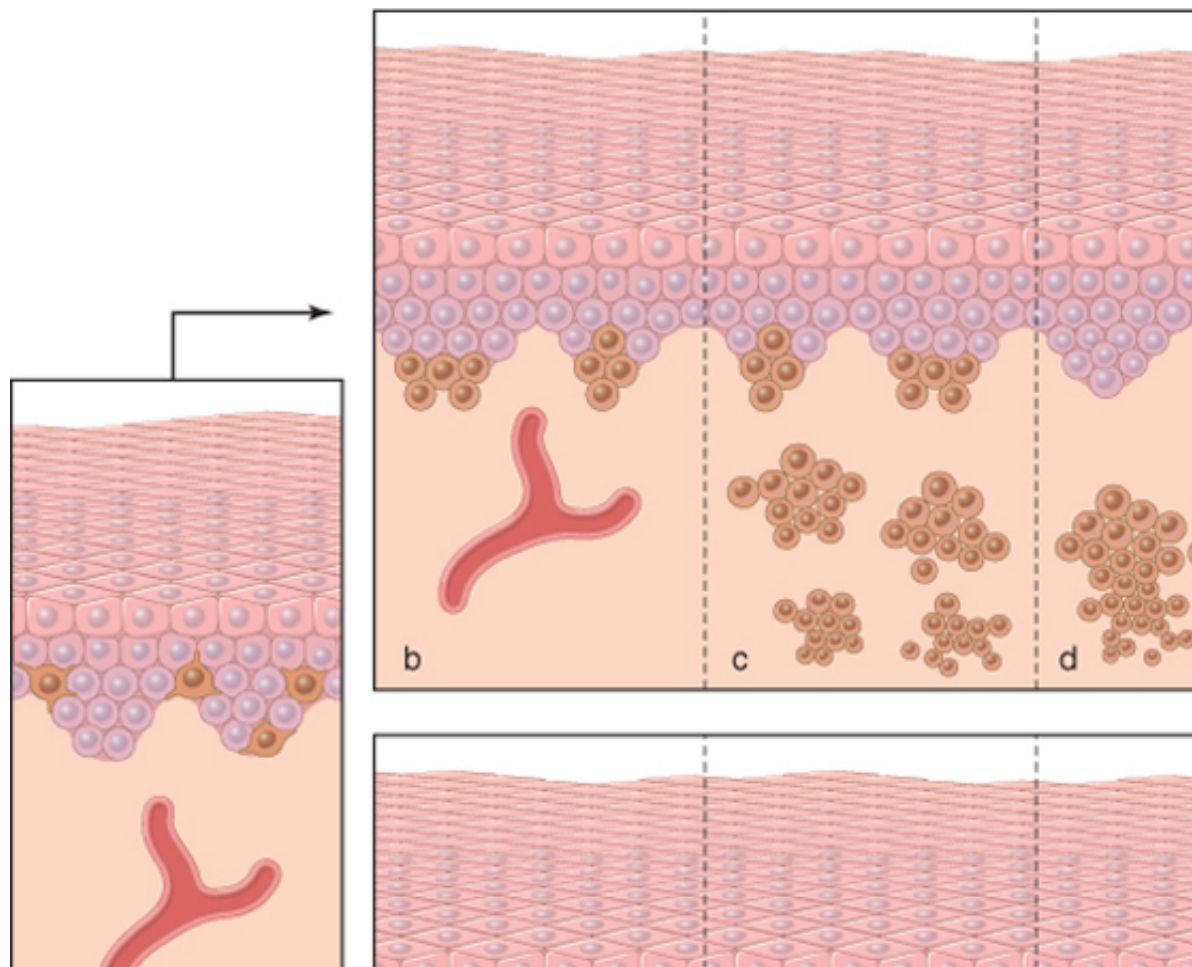




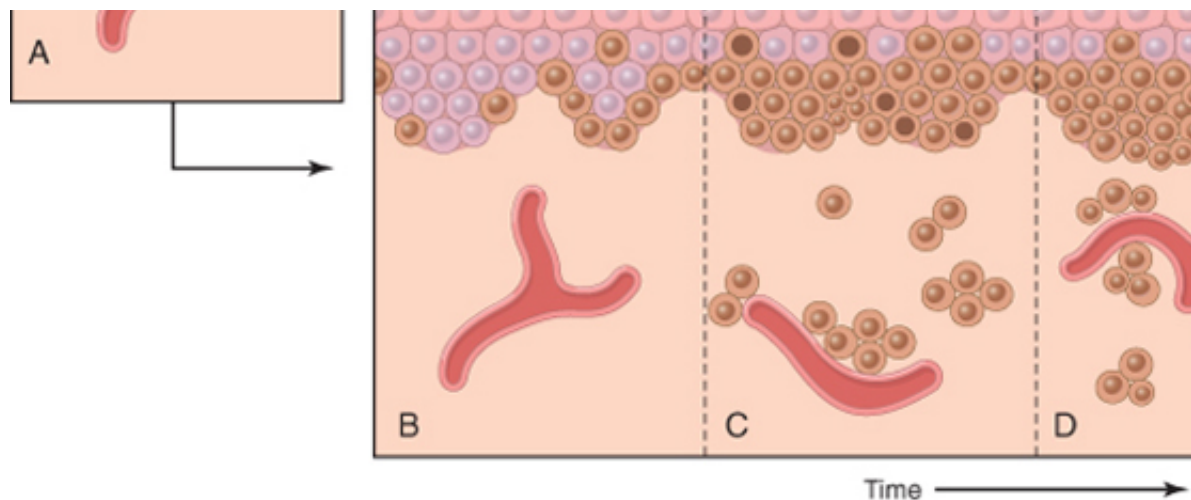
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Figure 22-21 Melanoma. **A**, Radial growth, showing irregular nested and single-cell spread of melanoma cells in the dermis (epidermis is on the right). **C**, Melanoma cells have a characteristic shape with prominent nucleoli. Mitoses, including atypical forms such as seen in the center of this field, are often encountered in melanoma, with irregular contours and pigmentation. Macular areas are early superficial (radial) growth, while elevated areas are nodular (vertical) growth).

Central to an understanding of the complicated histology of melanoma is the concept of *radial and vertical growth*. The *radial growth* indicates the initial tendency of a melanoma to grow horizontally within the epidermis (in situ) for a prolonged period (Fig. 22-21A). During this stage of growth, melanoma cells do not have the characteristic evidence of angiogenesis. With time, the pattern of growth assumes a *vertical component*, and the tumor invades the deeper dermal layers as an expansile mass lacking cellular maturation (Figs. 22-21B and 22-21C). Clinically, this is indicated by the development of a nodule in the relatively flat radial growth phase and correlates with the tumor's metastatic potential. The probability of metastasis is predicted by measuring the depth of invasion (Breslow thickness) and other factors such as lymphatic density, mitotic rate, and overlying ulceration. *Metastases involve not only regional lymph nodes but also virtually any other site that can be seeded by the hematogenous route*. Sentinel lymph node biopsy (removal of the first lymph node to which melanoma is thought to spread) at the time of surgery provides additional information on biological aggressiveness. In the first time many years after complete surgical excision of the primary tumor, suggesting a long







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Figure 22-22 Possible steps in development of melanocytic nevi and melanoma. **A**, Normal skin shows only scattered melanocytes. **B**, Compound nevus. **C**, Intradermal nevus. **D**, Intradermal nevus with neurotization (extreme maturation). **E**, Melanoma in vertical growth phase with metastatic potential. Note that no melanocytes are present in the epidermis in **E**. They are believed to arise de novo, perhaps using the same pathway as the nevi.

Most melanomas occur sporadically, but a few are hereditary (<5% to 10%). Molecular genetic analyses have provided important insights into the pathogenesis of melanoma. Germ-line mutations in the *p16* gene, which encodes p16<sup>INK4a</sup>, that regulates the G1-S transition of the cell cycle in a retinoblastoma protein (pRB)-dependent fashion, can also be silenced by methylation. Sporadic activating mutations in either *NRAS* or *BRAF* are also found but are generally mutually exclusive since *BRAF* functions downstream of *RAS*. Suppression of the *p53* gene, which is a tumor suppressor, is also found in primary melanomas, allowing activation of the *AKT* pathway that promotes cell proliferation. Surprisingly, deletion of *p53* is quite uncommon, perhaps because of overlapping cell cycle control functions of the melanocortin-1-receptor (*MC1R*) locus, associated with red hair, fair skin, and easy freckling, are also found in melanoma. As with other tumors, malignant transformation of melanocytes is a multistep process with activation of oncogenes and loss of tumor suppressor genes. The prevalence of these mutations varies in individual cases and research is directed toward finding agents that can target specific defects in these tumors.

### Morphology

Individual melanoma cells are usually considerably larger than nevus cells. They have irregular contours having chromatin characteristically clumped at the periphery of the nucleus. Prominent eosinophilic nucleoli are often described as "cherry red" (Fig. 22-21D). Malignant melanoma is characterized by nests or individual cells at all levels of the epidermis and as dermal expansion. These constitute the radial and vertical growth phases, respectively (see Figs. 22-21 and 22-22).

**The nature and extent of the vertical growth phase determine the biologic behavior of the tumor.** and thus it is important to observe and record these parameters and mitotic rate. Based on these variables in aggregate, accurate predictive statements regarding prognosis are possible.

### Clinical Features

Although most of these lesions arise in the skin, other less common sites of origin include the oral cavity, the meninges, and notably the eye. The following comments apply to cutaneous melanoma.

Clinically, melanoma of the skin is usually asymptomatic, although itching may be an early manifestation of the disease. A change in the color or size of a pigmented lesion is a common clinical feature. Unlike benign nevi, melanoma shows irregular pigmentation, appearing in shades of black, brown, red, dark blue, and gray (Fig. 22-21D). The border is often "notched." The main clinical warning signs of melanoma are (1) enlargement of a preexisting

mole, (3) development of a new pigmented lesion during adult life, (4) irregularity of the borders of color within a pigmented lesion. These principles are expressed in the so-called ABCs of melanoma and evolution (change of an existing nevus). It is vitally important to recognize and intervene in melanoma. The majority of superficial lesions are cured surgically, while melanomas that become metastatic have no effective therapy in most cases.

## SUMMARY

**Melanocytic Lesions, Benign and Malignant** Most *melanocytic nevi* tend to have mutations in just one gene, usually BRAF or less often NRAS, but the vast majority do not undergo malignant transformation. Most *dysplastic nevi* are best regarded as a risk rather than premalignant lesions. They are compound nevi with cytologically atypical cells but without highly aggressive malignancy; tumors only a few millimeters in thickness can progress to the death of the patient. In most cases, melanoma progresses from in situ to invasive (dermal) form. Characteristics of the dermal tumor such as tumor thickness and activity correlate strongly with overall survival.

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## 23 The Nervous System\*

MATTHEW P. FROSCH MD, PhD

### PATTERNS OF INJURY IN THE NERVOUS SYSTEM

The cellular constituents of the nervous system respond in different ways to various forms of injury.

#### *Markers of Neuronal Injury*

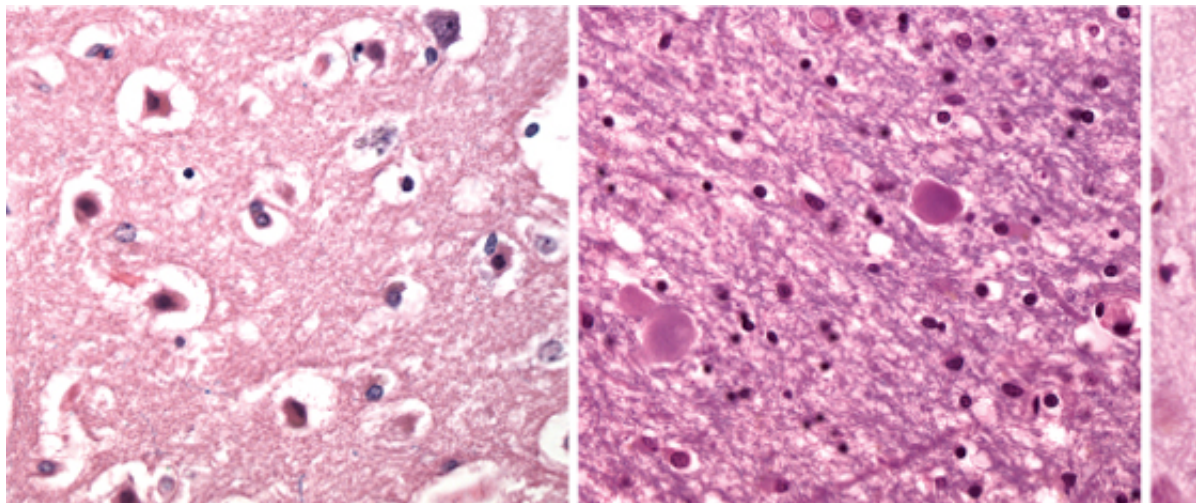
In response to injury, changes can be observed in neurons and their processes (axons and dendrites). In response to a hypoxic/ischemic insult, *acute neuronal injury* becomes evident even on routine hematoxylin and eosin (H & E) stain. It is shrinkage of the cell body, pyknosis of the nucleus, disappearance of the nucleolus, and loss of eosinophilia of the cytoplasm ("*red neurons*"). Often, the nucleus assumes the angulated shape of pyknosis. In cerebral ischemia, the process may progress to coagulative necrosis. Injured axons undergo swelling and show swellings (*spheroids*) can be recognized on H & E stains (Fig. 23-1B) and can be highlighted by staining for axonally transported proteins such as amyloid precursor protein. Axonal injury also leads to displacement of the nucleus, enlargement of the nucleolus, and dispersion of Nissl substance (from so-called *central chromatolysis*; Fig. 23-1C).

Many neurodegenerative diseases are associated with specific intracellular inclusions that help in diagnosis (e.g., neurofibrillary tangles in Parkinson disease and tangles in Alzheimer disease). In some neurodegenerative diseases, the axons become thickened and tortuous; these can be seen as *dystrophic neurites*.

Viral infections can form inclusions in neurons, just as they do in other cells of the body. With age, there is accumulation of lipofuscin in their cytoplasm and lysosomes (*lipofuscin*).

#### *Astrocytes in Injury and Repair*

Astrocytes are the principal cells responsible for repair and scar formation in the brain, a process called gliosis. In response to injury, astrocytes undergo both hypertrophy and hyperplasia. The nucleus enlarges and becomes vesicular, and the previously scant cytoplasm expands to a bright pink, somewhat irregular swath around an eccentric nucleus. The cell has stout, ramifying processes (*gemistocytic astrocyte*). There is minimal extracellular matrix deposition in the body, fibroblasts participate in healing after brain injury only to a limited extent (usually after abscesses). In settings of long-standing gliosis, astrocytes have less distinct cytoplasm and appear more foamy. *Rosenthal fibers* are thick, elongated, brightly eosinophilic protein aggregates that can be found in astrocytes and in some low-grade gliomas.





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Figure 23-1 Patterns of neuronal injury. **A**, Acute hypoxic/ischemic injury in cerebral cortex, where the individual neurons are intensely stained by eosin, leading to the term "red neurons." **B**, Axonal spheroids are visible as bright, eosinophilic, rounded structures. **C**, With axonal injury there can be swelling of the cell body and peripheral dispersal of the axonal transport (H&E).

*Corpora amylacea* represent a degenerative change in astrocytes and occur in increasing number with age. They are faintly basophilic, periodic acid-Schiff (PAS)-positive, concentrically lamellated aggregates of polypeptides, and are located wherever there are astrocytic end processes, especially in the subpial and periventricular regions.

#### Other Cells

*Oligodendrocytes*, which produce myelin, have a limited repertoire of morphologic changes, apart from those seen in multiple sclerosis. In progressive multifocal leukoencephalopathy, viral inclusions can be seen in the nuclei of oligodendrocytes, and the nuclei may appear enlarged and homogeneous.

*Ependymal cells* line the ventricular system and are located in the region of the obliterated central sulci. Ependymal cells are often associated with a local proliferation of subependymal astrocytes to produce the so-called *ependymal granulations*. Certain infectious agents, particularly cytomegalovirus (CMV), and viral inclusions may be seen in them.

*Choroid plexus* is responsible for the secretion of CSF and is in continuity with the ependyma, extending into the ventricular system. It is covered by a specialized epithelial covering with a fibrovascular stroma that may contain meningeal cells.

*Microglia* are bone marrow-derived cells that function as the phagocytes of the CNS. When activated by trauma, infection, or hemorrhage, they proliferate and become more evident. They may be recognizable as activated macrophages in organizing infarct, or hemorrhage, or they develop elongated nuclei (*rod cells*) in neurosyphilis or, when they form aggregates at sites of tissue injury, they are termed *microglial nodules*. Similar collections of microglia around portions of dying neurons, termed *neuronophagia*.



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## PATTERNS OF INJURY IN THE NERVOUS SYSTEM

The cellular constituents of the nervous system respond in different ways to various forms of injury.

### Markers of Neuronal Injury

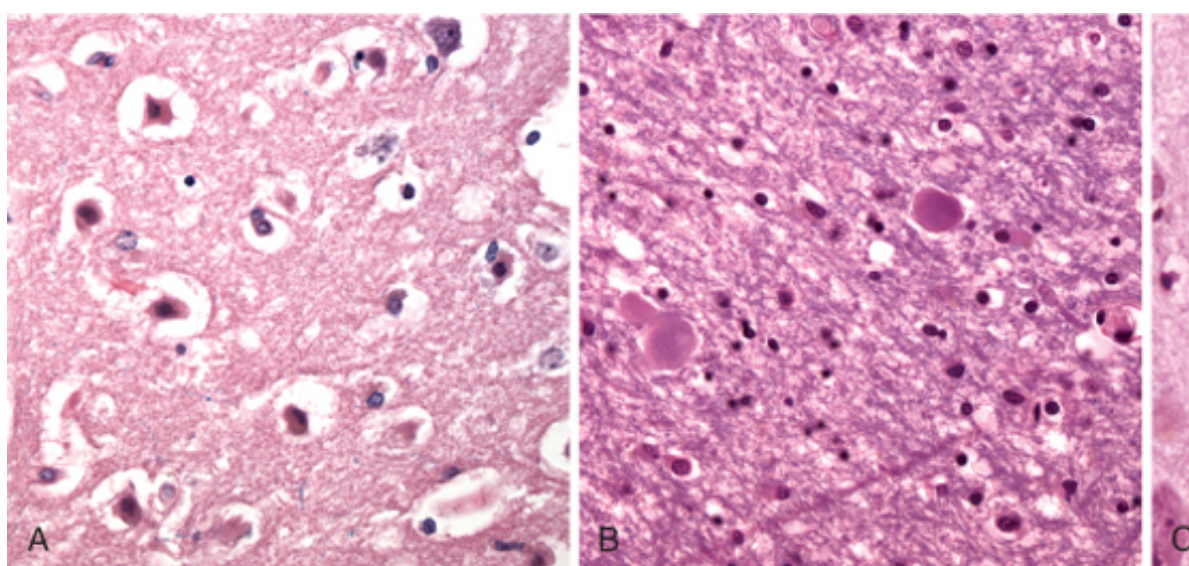
In response to injury, changes can be observed in neurons and their processes (axons and dendrites). In response to hypoxic/ischemic insult, *acute neuronal injury* becomes evident even on routine hematoxylin and eosin (H & E) stain. It is characterized by shrinkage of the cell body, pyknosis of the nucleus, disappearance of the nucleolus, and loss of eosinophilia of the cytoplasm ("*red neurons*"). Often, the nucleus assumes the angulated shape of a pyknotic nucleus. In cerebral ischemia, injured axons undergo swelling and show swellings (*spheroids*) can be recognized on H & E stains (Fig. 23-1B) and can be highlighted by silver stains. Axonal injury also leads to cell body displacement of the nucleus, enlargement of the nucleolus, and dispersion of Nissl substance (so-called *central chromatolysis*; Fig. 23-1C).

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Figure 23-1 Patterns of neuronal injury. ▲ Acute hypoxic/ischemic injury in cerebral cortex where the individual

Figure 20-14 Patterns of neuronal injury. **A**, Acute hypoxic-ischemic injury in cerebral cortex, where the individual neurons are swollen and their nuclei are pyknotic. They also are prominently stained by eosin, leading to the term "red neurons." **B**, Axonal spheroids are visible as bright eosinophilic masses, indicating disruption of axonal transport (H&E). **C**, With axonal injury there can be swelling of the cell body and peripheral dispersal of the

*Corpora amylacea* represent a degenerative change in astrocytes and occur in increasing number with age. They are faintly basophilic, periodic acid-Schiff (PAS)-positive, concentrically lamellated aggregates of polysaccharides, 1–10 μm, and are located wherever there are astrocytic end processes, especially in the subpial and periventricular regions.

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## EDEMA, HERNIATION, AND HYDROCEPHALUS

The brain and spinal cord exist within a rigid compartment defined by the skull and spinal canal, and blood vessels pass through this structure via specific foramina, but the brain is confined to the cranial vault. The delicate CNS within such a protective environment is obvious, yet these rigid confines provide little leeway in disease states. Disorders that upset this delicate balance include generalized cerebral edema, mass lesions.

### Cerebral Edema

Cerebral edema is the accumulation of excess fluid within the brain parenchyma. This term should not be confused with an increase in CSF volume within all or part of the ventricular system. There are two underlying mechanisms of cerebral edema that often occur together particularly when there is generalized injury.

*Vasogenic edema* occurs when the integrity of the normal blood-brain barrier is disrupted. Fluid shifts from the vascular compartment into the intercellular spaces of the brain. Vasogenic edema is caused because of abnormal permeability of vessels adjacent to inflammation or tumors or general edema because of an increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury. It is seen in an individual with a generalized hypoxic/ischemic insult or with exposure to some toxins.

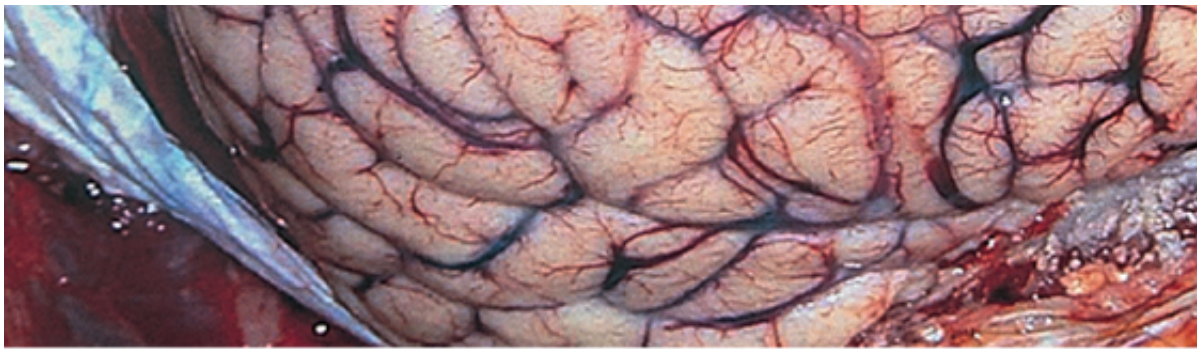
### Morphology

The edematous brain is softer than normal and often appears to "overflow" the cranium. In severe edema the gyri are flattened, the intervening sulci are narrowed, and the ventricles are compressed (Fig. 23-2).

### Hydrocephalus







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Figure 23-2 Cerebral edema. The surfaces of the gyri are flattened as a result of compression of the expanding brain against the skull. Such changes are associated with a dangerous increase in intracranial pressure.

After being produced by the choroid plexus within the ventricles, cerebrospinal fluid (CSF) circulates through the foramina of Luschka and Magendie. CSF fills the subarachnoid space around the brain, providing the cushioning of the nervous system within its bony confines. The balance between CSF generation and resorption keeps the volume of this fluid stable. *Hydrocephalus* is an excessive accumulation of CSF within the ventricular system. Most cases occur as a consequence of impaired flow of CSF. In some instances (e.g., tumors of the choroid plexus), overproduction of CSF may be responsible. When the cranial sutures are closed, there is enlargement of the head. Hydrocephalus developing after birth is associated with expansion of the ventricles and increased intracranial pressure, without a change in the volume of brain tissue.

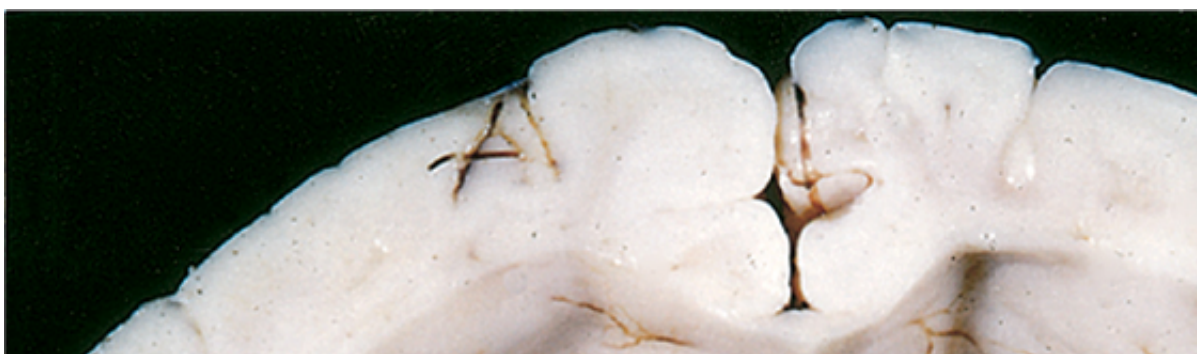
If there is an obstacle to the flow of CSF within the ventricular system, then a portion of the ventricular system becomes dilated. This pattern is referred to as *noncommunicating hydrocephalus* and is most commonly seen in the third ventricle and aqueduct of Sylvius. In *communicating hydrocephalus* all of the ventricular system is enlarged; here the CSF is in free communication with the subarachnoid space and resorption of CSF is normal.

The term *hydrocephalus ex vacuo* refers to dilation of the ventricular system with a compensatory loss of brain parenchyma, as may occur after infarcts or with a degenerative disease.

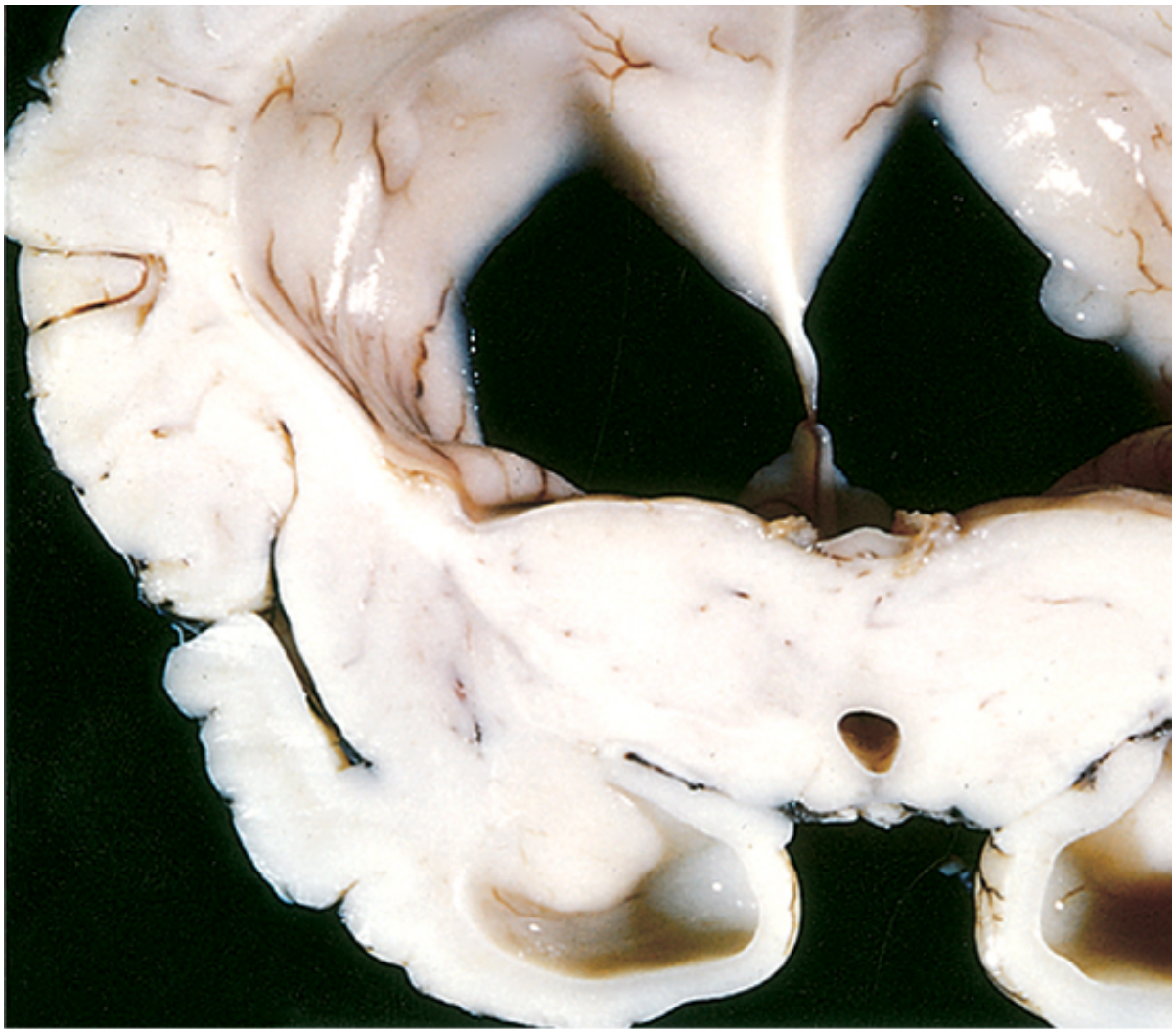
### Herniation

When the volume of brain tissue increases beyond the limit permitted by compression of veins and the pressure may rise. Because the cranial vault is subdivided by rigid dural folds (falx and tentorium), the brain is displaced in relation to these partitions. If the expansion is sufficiently severe, herniation will occur. It is named either by the part of the brain that is displaced or the structure across which it moves. The usual consequence is compromise of the blood supply to the "pushed" tissue, resulting in infarction. This often leads to death.

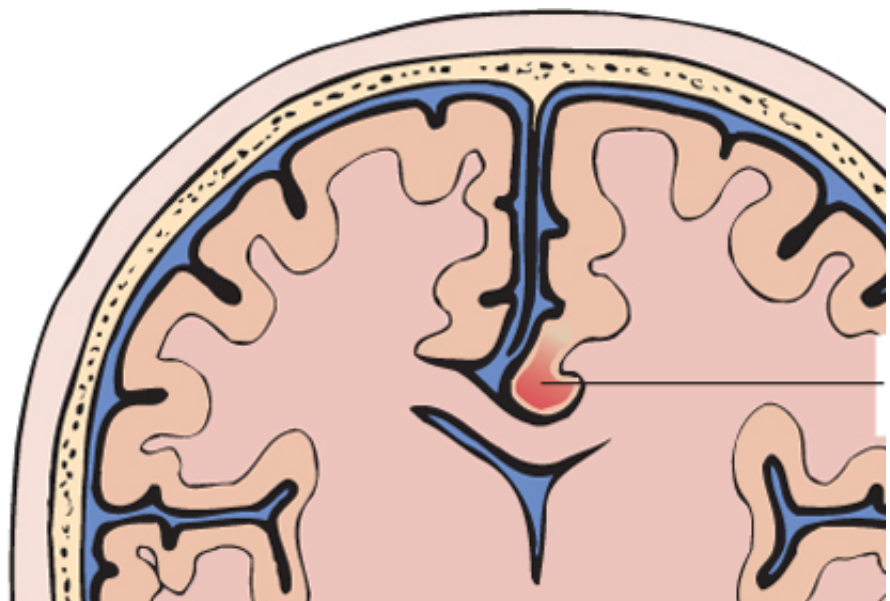
*Subfalcine (cingulate) herniation* occurs when unilateral or asymmetric expansion of a cerebral hemisphere causes the brain to shift under the edge of falx. This may be associated with compression of branches of the anterior cerebral artery.

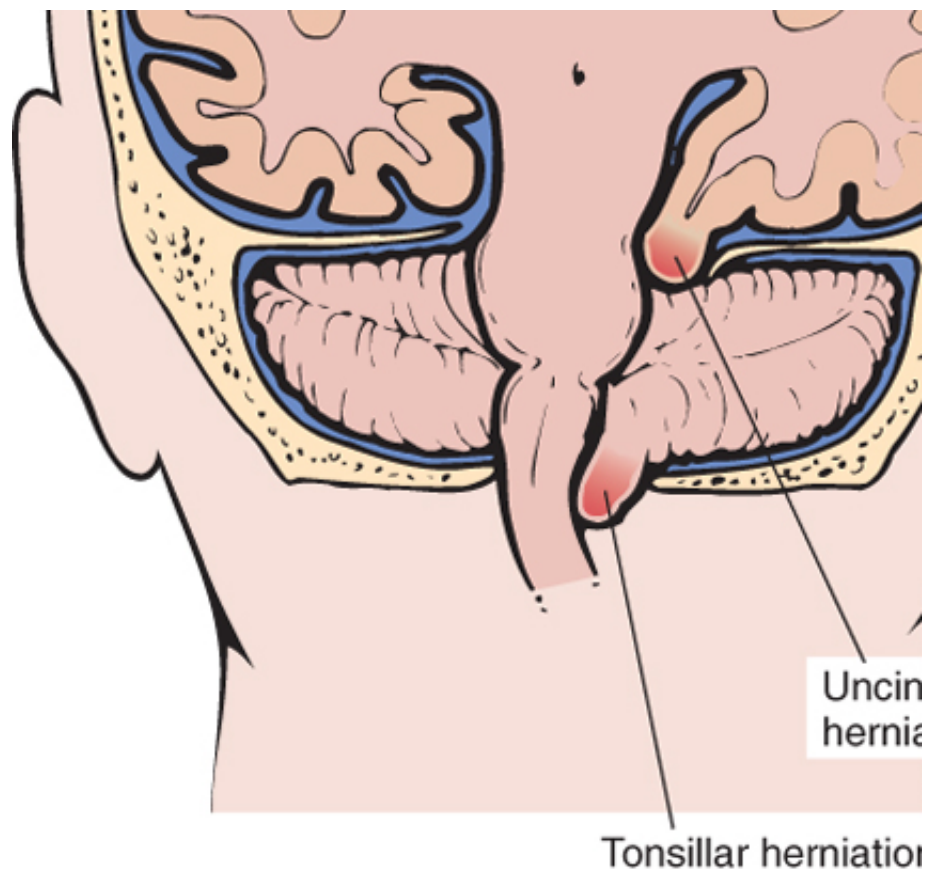






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Figure 23-3 Hydrocephalus. Dilated lateral ventricles seen in a coronal section through

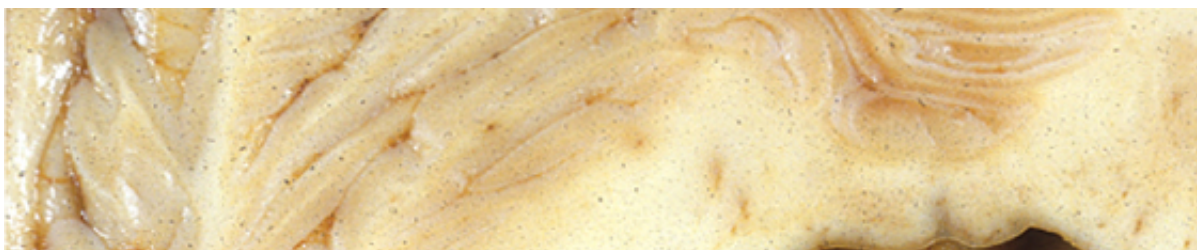


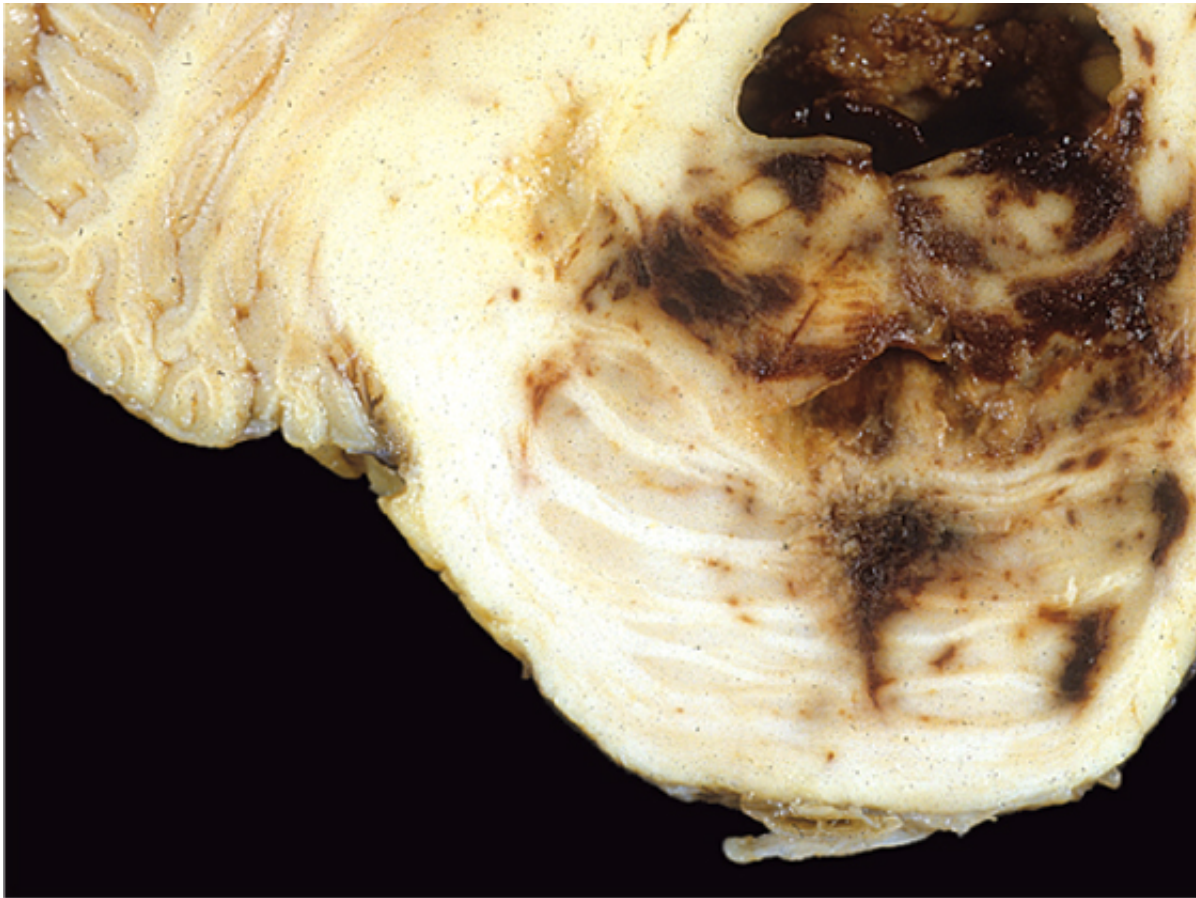


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 Figure 23-4 Patterns of brain herniation: subfalcine (cingulate), transtentorial (uncinate, mesial temporal), and tonsillar (Fig. 23-5). (Engl J Med 293:706, 1975.)

*Transtentorial (uncinate)* herniation occurs when the medial aspect of the temporal lobe is compressed against the tentorium. As the temporal lobe is displaced, the third cranial nerve is compromised, resulting in ipsilateral pupillary dilation ("blown pupil"). The posterior cerebral artery may also be compressed, resulting in contralateral homonymous hemianopia. When the extent of herniation is severe, the cerebral peduncle may be compressed, resulting in hemiparesis ipsilateral to the side of the herniation. Typically, this ipsilateral hemiparesis can be a false localizing sign if the patient has a lesion in the opposite, unaffected hemisphere. The changes in the peduncle in transtentorial herniation are often accompanied by hemorrhagic lesions in the midline and paramedian areas, known as *Kernohan's wedge*. Progression of transtentorial herniation is often accompanied by hemorrhagic lesions in the midline and paramedian areas, known as *Kernohan's wedge*. These linear or flame-shaped lesions usually occur in the midline and paramedian areas due to tearing of penetrating veins and arteries supplying the upper brain stem. The presence of these lesions is a poor prognosis.

Tonsillar herniation refers to displacement of the cerebellar tonsils through the foramen magnum. It is a life-threatening condition because it causes brain stem compression and compromises vital respiratory and cardiovascular functions.





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Figure 23-5 Duret hemorrhage. As mass effect displaces the brain downwards, there is disruption of the vessels and subsequent hemorrhage.

## SUMMARY

**Edema, Herniation, and Hydrocephalus** Cerebral edema is the accumulation of fluid in the brain parenchyma. Hydrocephalus is an increase in CSF volume within the ventricular system. Increases in tissue volume of the brain (as a result of increased CSF volume or hemorrhage) increase the pressure inside the fixed capacity of the skull. Increased pressure can damage the brain either by decreasing perfusion or by displacing tissue across the skull or through openings in the skull (herniations).



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## CEREBROVASCULAR DISEASES

Cerebrovascular disease is the third leading cause of death (after heart disease and cancer) in the prevalent neurologic disorder in terms of both morbidity and mortality. The term *cerebrovascular* disease of the brain caused by a pathologic process involving blood vessels. The three basic processes are (1) thrombotic occlusion of vessels, (2) embolic occlusion of vessels, and (3) vascular rupture. The first two share many characteristics, both resulting in same-loss of oxygen and metabolic substrates resulting in brain infarction. Thrombosis and embolism affect specific regions of the brain, depending on the vessel involved. A similar pattern of injury occurs during hypoperfusion (or delivery of oxygen and metabolic substrate). Hemorrhage accompanies rupture of vessels, as well as secondary ischemic injury. "Stroke" is the clinical designation that applies to all these conditions occurring acutely.

### Hypoxia, Ischemia, and Infarction

The brain requires a constant delivery of [glucose](#)<sup>®</sup> and oxygen from the blood. Although the brain is only 2% of body weight, it receives 15% of the resting cardiac output and accounts for 20% of the total body oxygen consumption. The brain remains constant over a wide range of blood pressure and intracranial pressure because of autoregulation. The brain is a highly aerobic tissue, with oxygen being the limiting substance. The brain may be deprived of oxygen by several mechanisms: *functional hypoxia* in a setting of a low partial pressure of oxygen; impaired oxygen delivery to tissue; or *ischemia*, either *transient* or *permanent*, after interruption of the normal circulatory flow. Ischemia results from a reduction in perfusion pressure, as in hypotension, or secondary to vascular obstruction, or

### Global Cerebral Ischemia

This pattern of widespread ischemic/hypoxic injury occurs when there is a generalized reduction in cerebral perfusion pressures of less than 50mmHg, such as in cardiac arrest, shock, and severe hypotension. The severity of the insult. When mild, there may be only a transient postischemic confusional state, which resolves. Irreversible damage of CNS tissue does occur in some individuals who suffer mild or transient global ischemia. Neurons are more sensitive to hypoxia than are glial cells. There is also variability in the susceptibility of different regions of the CNS; pyramidal cells of the Sommer sector (CA1) of the hippocampus, Purkinje cells of the cerebellum, and neurons in the neocortex are the most susceptible to ischemia of short duration. In severe global ischemia, death, irrespective of regional vulnerability, occurs. Individuals who survive in this state often remain in a deeply comatose (persistent vegetative state). Other patients meet the clinical criteria for "brain death" (cortical injury (isoelectric, or "flat," electroencephalogram) and brain stem damage, including absence of reflexes). Patients with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually recovering resulting in the so-called "respirator brain."

### Morphology

In the setting of global ischemia, the brain is swollen, with wide gyri and narrowed sulci. The histopathologic changes in ischemic injury (infarction) are grouped into three categories. **Early changes**, occurring within minutes of the insult, include acute neuronal cell change (red neurons; see [Fig. 23-1A](#)) characterized by eosinophilic cytoplasm, microvacuolization, followed by cytoplasmic eosinophilia, and later nuclear pyknosis. **Intermediate changes** occur somewhat later in astrocytes and oligodendroglia. After this, the reaction begins with infiltration by neutrophils ([Fig. 23-6A](#)). **Subacute changes**, occurring a few days to weeks after the insult, include necrosis of tissue, influx of macrophages, vascular proliferation, and reactive gliosis. **Repair**, seen after 2 weeks, is characterized by removal of all necrotic tissue, loss of normal architecture, and gliosis ([Fig. 23-6C](#)). In the cerebral cortex the neuronal loss and gliosis are most prominent in the neocortex, with preservation of some layers and involvement of the hippocampus and cerebellum. Pseudolaminar necrosis.

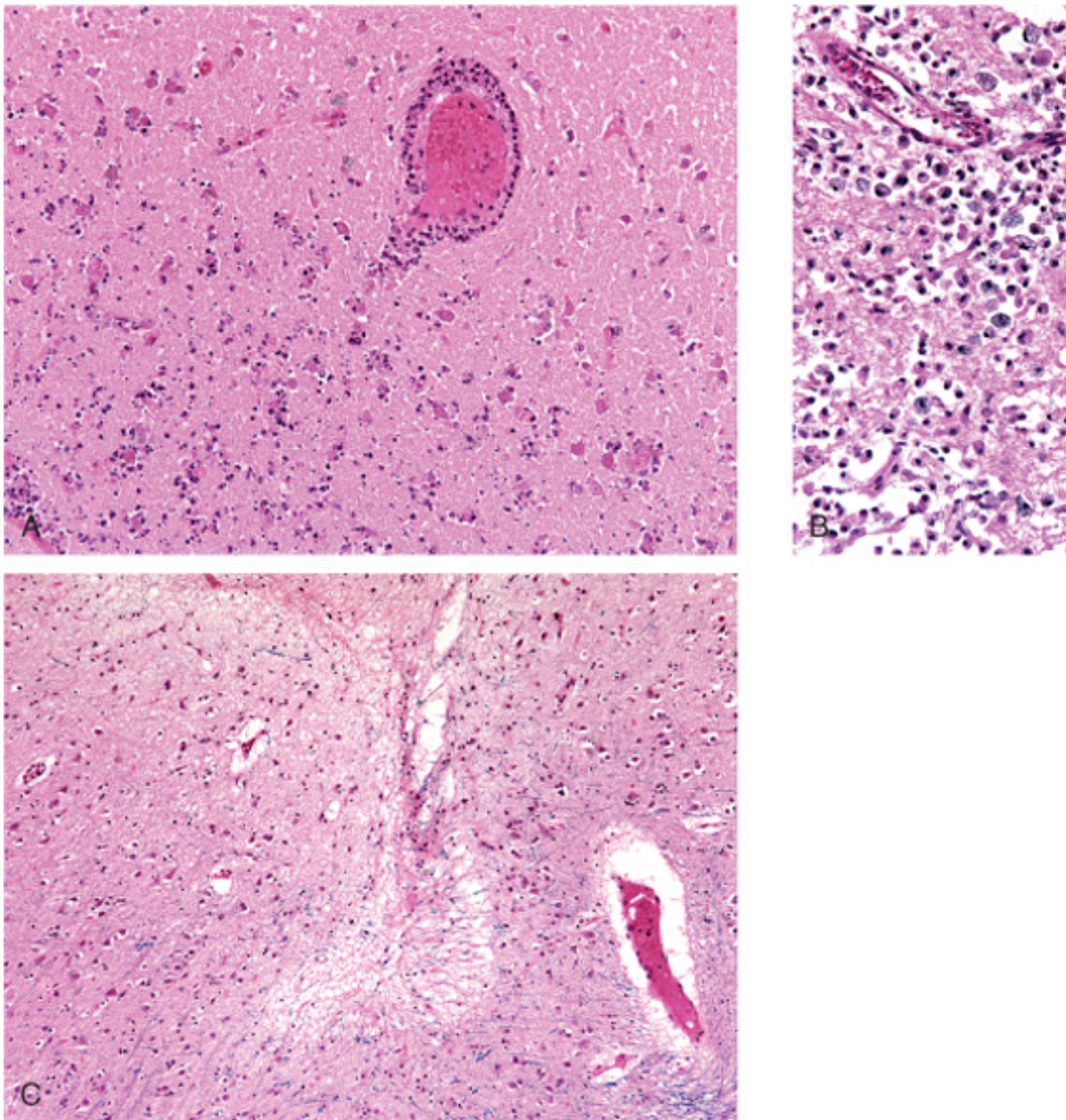
**Border zone ("watershed") infarcts** are wedge-shaped areas of infarction that occur in those re-



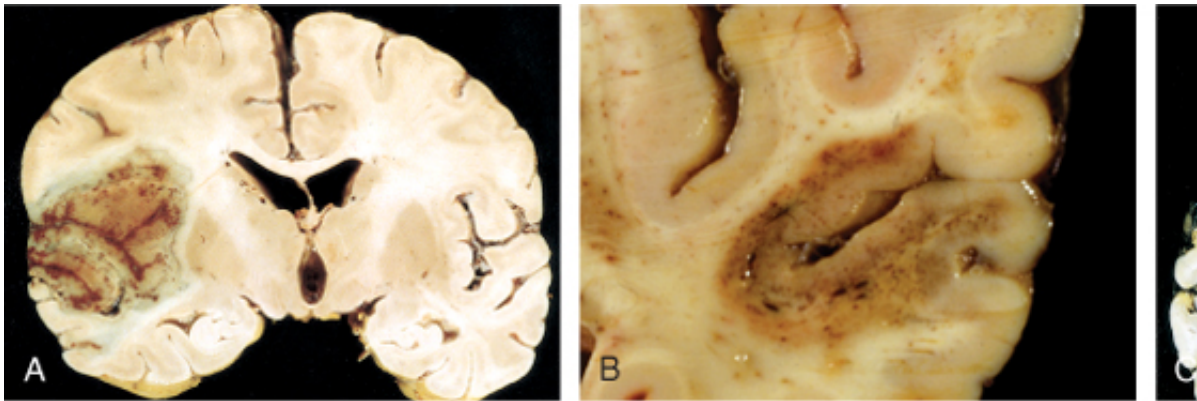
**Border zone ( watershed ) infarcts** are wedge-shaped areas of infarction that occur in those regions at the most distal fields of arterial perfusion. In the cerebral hemispheres, the border zone between artery distributions is at greatest risk. Damage to this region produces a band of necrosis over the lateral to the interhemispheric fissure. Border zone infarcts are usually seen after hypotensive episodes.

### ***Focal Cerebral Ischemia***

Cerebral arterial occlusion leads to focal ischemia and-if sustained-to infarction of CNS tissue in the brain. The size, location, and shape of the infarct and the extent of tissue damage that results are determined by the adequacy of collateral flow. The major source of collateral flow is the circle of Willis; blood flows over the surface of the brain through cortical-leptomeningeal anastomoses. In contrast, there is little penetrating vessels supplying structures such as the thalamus, basal ganglia, and deep white matter.



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 Figure 23-6 Cerebral infarction. **A**, Infiltration of a cerebral infarction by neutrophils begins at the edges of the lesion. After about 10 days, an area of infarction is characterized by the presence of macrophages and surrounding reactive gliosis. The infarcted areas are seen as areas of tissue loss with a small amount of residual gliosis.



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Figure 23-7 Cerebral infarction. **A**, Section of the brain showing a large, discolored, focally hemorrhagic region (hemorrhagic, or red, infarction). **B**, An infarct with punctate hemorrhages, consistent with ischemia-reperfusion injury. The infarct shows destruction of cortex and surrounding gliosis.

Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to *in situ* or from a distant source. Overall, embolic infarctions are more common. Cardiac mural thrombi are a frequent cause of embolism, and atrial fibrillation are important predisposing factors. Thromboemboli also arise in arterial plaques within the carotid arteries. Other sources of emboli include paradoxical emboli, particularly those associated with cardiac surgery; and emboli of other material (tumor, fat, or air). The territory of the middle cerebral artery-the direct extension of the internal carotid artery-is most frequently affected by embolic infarction. The territory of the anterior cerebral artery is most frequently affected by thrombotic infarction. The territory of the posterior cerebral artery is most frequently affected by thrombotic infarction. The territory of the vertebral artery is most frequently affected by thrombotic infarction. The territory of the basilar artery is most frequently affected by thrombotic infarction. The territory of the posterior inferior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the anterior inferior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the superior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the inferior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the middle cerebellar artery is most frequently affected by thrombotic infarction. The territory of the anterior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the posterior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the middle cerebellar artery is most frequently affected by thrombotic infarction. The territory of the anterior cerebellar artery is most frequently affected by thrombotic infarction. The territory of the posterior cerebellar artery is most frequently affected by thrombotic infarction.

The majority of thrombotic occlusions causing cerebral infarctions are due to *atherosclerosis*; the most common sites are the carotid bifurcation, the origin of the middle cerebral artery, and at either end of the basilar artery. Thrombi may develop superimposed thrombosis, accompanied by anterograde extension, fragmentation, and dislodgment.

Infarcts can be divided into two broad groups based on their macroscopic and corresponding radiologic appearance. *Nonhemorrhagic infarcts* can be treated with thrombolytic therapies, if identified shortly after presentation. *Hemorrhagic infarcts* are characterized by multiple, sometimes confluent, petechial hemorrhages (Fig. 23-7B) secondary to reperfusion of ischemic tissue, either through collaterals or after dissolution of intravascular thrombi.

### Morphology

The macroscopic appearance of a **nonhemorrhagic infarct** changes in time. During the first 24 hours of irreversible injury, little can be observed. By 48 hours the tissue becomes pale, soft, and swollen. The corticomedullary junction becomes indistinct. From 2 to 10 days the brain becomes edematous, and the previously ill-defined boundary between normal and abnormal tissue becomes more distinct. From 10 days to 3 weeks the edema resolves in the adjacent tissue that has survived. From 10 days to 3 weeks eventually leaving a fluid-filled cavity lined by dark gray tissue, which gradually expands and is removed (Fig. 23-7C).

Microscopically, the tissue reaction follows a characteristic sequence: **After the first 24 hours**, there is neuronal change (red neurons; see Fig. 23-1A) and both cytotoxic and vasogenic edema. **By 48 hours**, there is loss of the usual tinctorial characteristics of white and gray matter structures. Endothelial cells swell, and myelinated fibers begin to disintegrate. **Until 48 hours**, there is neutrophilic emigration followed by mononuclear phagocytic cells in the ensuing 2 weeks. **By 2 weeks**, containing myelin breakdown products or blood may persist in the lesion for months. **By 3 weeks**, of phagocytosis and liquefaction proceeds, astrocytes at the edges of the lesion proliferate, divide, and develop a prominent network of protoplasmic extensions.

**After several months** the striking astrocytic nuclear and cytoplasmic enlargement and the formation of a cavity. astrocyte processes form a dense feltwork of glial fibers admixed with new neurons.



cavity, astrocyte processes form a dense network of glial fibers admixed with new perivascular connective tissue fibers. In the cerebral cortex the cavity is delimited from the subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of the arachnoid. The pia and the layers of the arachnoid are not affected and do not contribute to the healing process.

The microscopic picture and evolution of **hemorrhagic infarction** parallel ischemic infarction. The addition of blood extravasation and resorption. In persons receiving anticoagulant therapy, hemorrhagic infarcts may be associated with extensive intracerebral hematomas.

### **Intracranial Hemorrhage**

Hemorrhage within the skull can occur in a variety of locations, and each location is associated with a specific pattern of injury. Hemorrhages within the brain itself can occur secondary to hypertension or other forms of vascular disease. Hemorrhages in a specific lesion like an arteriovenous malformation, a cavernous malformation, or an intraparenchymal hemorrhage are most commonly seen with aneurysms but occur also with other vascular malformations. Hemorrhages on the dura (in either subdural or epidural spaces) make up a pattern associated with trauma.

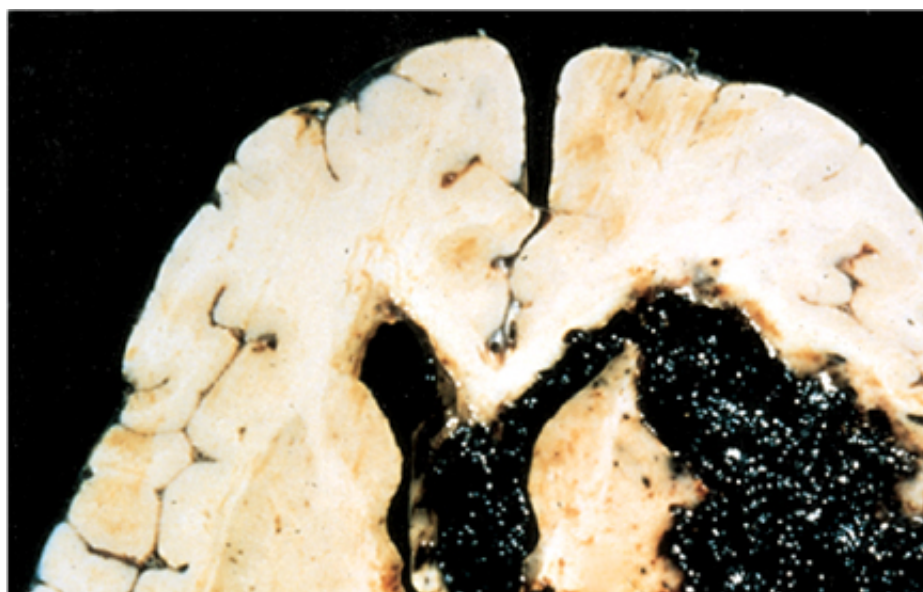
### **Primary Brain Parenchymal Hemorrhage**

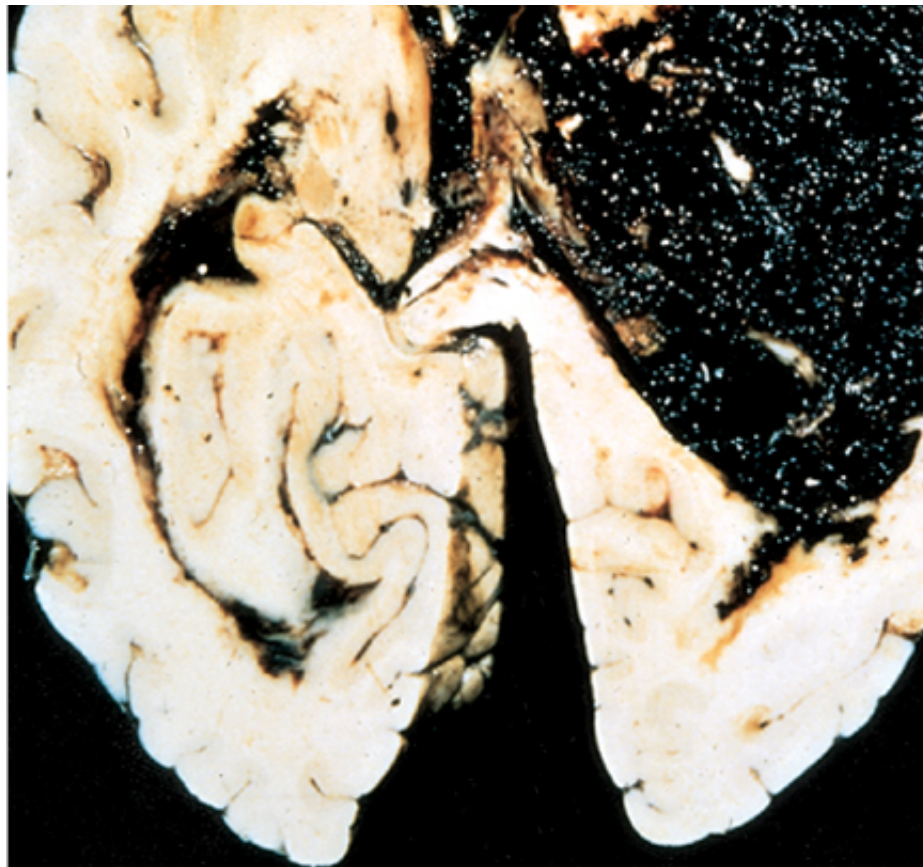
Spontaneous (nontraumatic) intraparenchymal hemorrhages occur most commonly in mid to late life, after 60 years of age. Most are caused by rupture of a small intraparenchymal vessel. Hypertension is the most common cause. Brain hemorrhage accounts for roughly 15% of deaths among individuals with chronic hypertension. Hypertensive hemorrhages typically occur in the basal ganglia, thalamus, pons, and cerebellum (Fig. 23-8).

Intracerebral hemorrhage can be clinically devastating when it affects large portions of the brain and causes a mass effect. Alternatively, it can affect small regions and be clinically silent. Over weeks or months there is a gradual resolution of the hematoma, sometimes with considerable clinical improvement. Again, the location and size of the bleed will determine the clinical outcome.

### **Morphology**

Acute hemorrhages are characterized by extravasation of blood with compression of the surrounding brain parenchyma. Old hemorrhages show an area of cavitory destruction of brain with a rim of gliosis and discoloration. On microscopic examination, the early lesion consists of a central core of blood surrounded by a rim of brain tissue showing anoxic neuronal and glial changes as the edema resolves, pigment- and lipid-laden macrophages appear, and proliferating astrocytes become visible at the periphery of the lesion. The cellular events then follow the same pattern as after cerebral infarction.





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Figure 23-8 Cerebral hemorrhage. Massive hypertensive hemorrhage rupturing into

### Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a disease in which amyloidogenic peptides-typically the  $\beta$ -amyloid (see below)-deposit in the walls of medium- and small-caliber meningeal and cortical vessels. This deposit thickens the vessel wall and increases the risk of hemorrhage. Since CAA is limited to leptomeningeal and cortical vessels, hemorrhages associated with CAA have a distribution that is predominantly in the cerebral cortex and deep gray structures, as opposed to the deep white matter and deep gray structures seen in hypertensive hemorrhages. CAA-associated hemorrhages are often referred to as *lobar hemorrhages*. As in other locations, amyloid in the vessel walls can be identified by Congo red staining, which gives the vessel walls a pipe-like appearance.

### Subarachnoid Hemorrhage and Saccular Aneurysms

The most frequent cause of clinically significant subarachnoid hemorrhage is rupture of a *saccular aneurysm*. Subarachnoid hemorrhage may also result from vascular malformation, trauma (in which case it is usually a diffuse injury), rupture of an intracerebral hemorrhage into the ventricular system, hematologic disorders, or drugs that affect coagulation.

Rupture can occur at any time, but in about one-third of cases it is associated with acute increase in intracranial pressure, such as straining at stool or sexual orgasm. Blood under arterial pressure is forced into the subarachnoid space, causing a sudden, excruciating headache (classically described as "the worst headache I've ever had") and vomiting. About 25% and 50% of individuals die with the first rupture, although those who survive typically improve. Recurring bleeding is common in survivors; it is currently not possible to predict which individuals will have a poor prognosis, which worsens with each episode of bleeding.

About 90% of saccular aneurysms occur in the anterior circulation near major arterial branch points. About 20% to 30% of cases. Although they are sometimes referred to as *congenital*, they are not present from birth but result from underlying defects in the vessel media. Besides an association with disorders of extracellular matrix, saccular aneurysms are also associated with autosomal dominant polycystic kidney disease.



Overall, aneurysms have a roughly 1.3% per year rate of bleeding. However, the probability of rupture is much higher for aneurysms greater than 10 mm, which have a roughly 50% risk of bleeding per year. In the event of an intracerebral hemorrhage, there is a risk of additional ischemic injury from vasospasm involving other vessels. Following a subarachnoid hemorrhage, meningeal fibrosis and scarring occur, sometimes leading to obstruction of CSF flow pathways or CSF resorption.

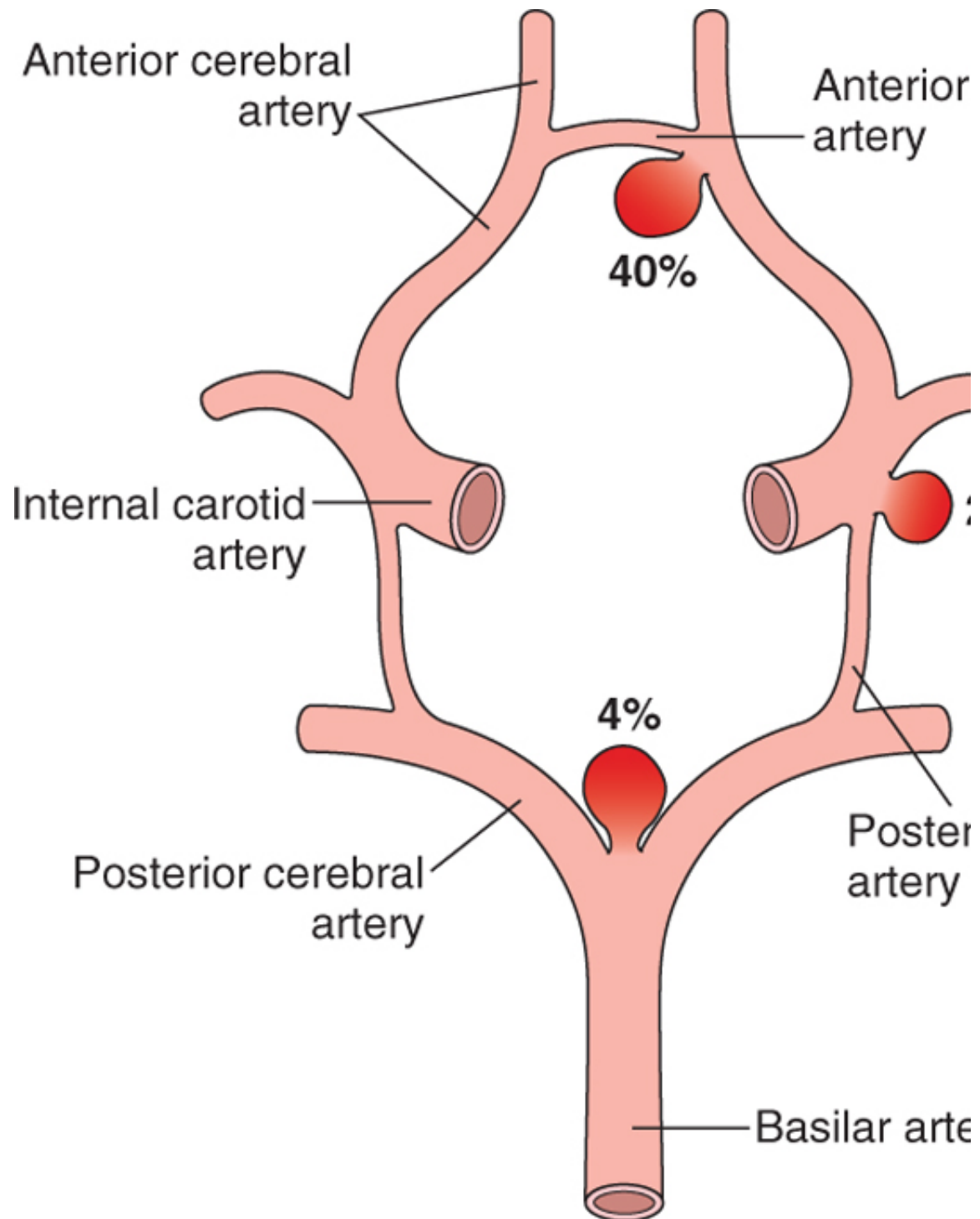


Figure 23-9 Relative frequency of common sites of saccular (berry) aneurysms in the

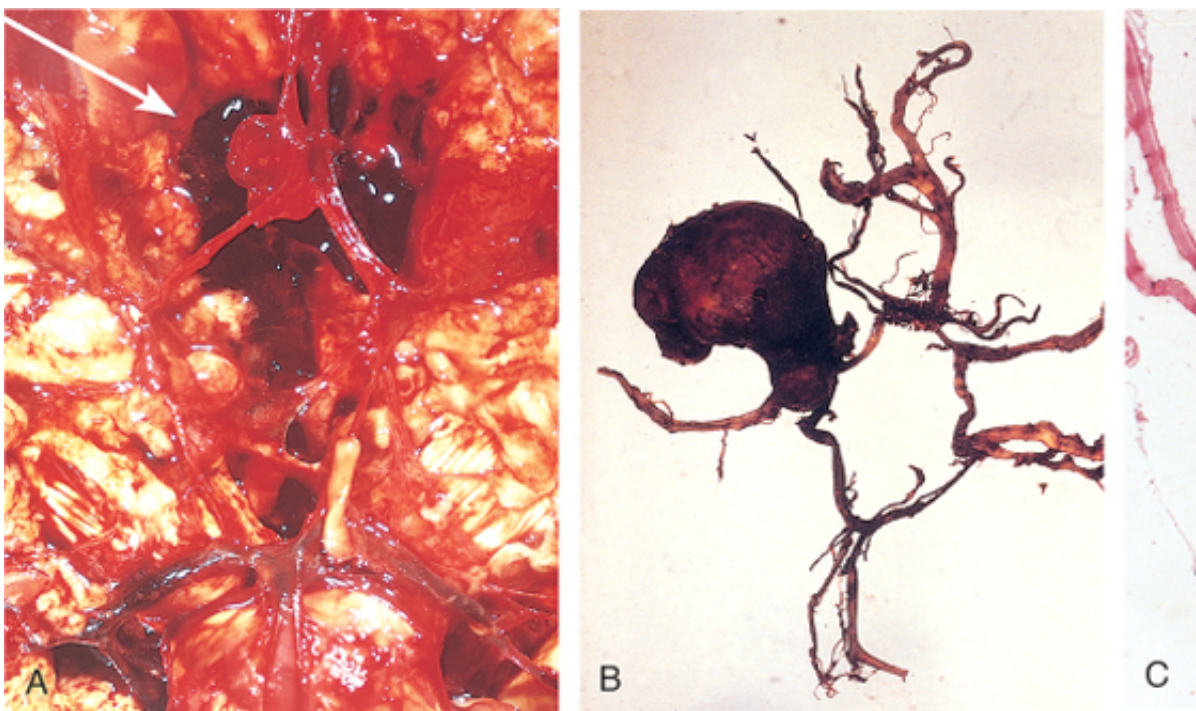
### Morphology

An unruptured saccular aneurysm is a thin-walled outpouching of an artery. At the neck of the aneurysm, the muscular wall and intimal elastic lamina stop short and are absent from the aneurysm, which is made up of thickened hyalinized intima. The adventitia covering the sac is continuous with the adventitia of the parent artery (Fig. 23-10). Rupture usually occurs at the apex of the sac with extravasation of blood into the subarachnoid space, the substance of the brain, or both.

While saccular aneurysms are the most common type of intracranial aneurysm, other types include fusiform (usually of the basilar artery), mycotic, traumatic, and dissecting aneurysms. These latter three, as with saccular aneurysms, are usually associated with anterior circulation. They usually present with cerebral infarction from vascular occlusion instead of hemorrhage.

### Vascular Malformations

Vascular malformations of the brain are classified into four principal types based on the nature of the malformation: *arteriovenous malformations (AVM)*, the most common, *cavernous angiomas*, *capillary telangiectasias*, and *venous angiomas*. AVMs are more frequent in males than in females; the lesion is most often recognized clinically between the ages of 10 and 40 years. The clinical picture is usually that of a hemorrhagic disorder, an intracerebral hemorrhage, or a subarachnoid hemorrhage. Large AVMs occurring in the posterior circulation can lead to congestive heart failure because of blood shunting directly from arteries to veins. The risk of rupture is the most dangerous type of vascular malformation.



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Figure 23-10 Saccular aneurysms. **A**, View of the base of the brain, dissected to show the circle of Willis with an aneurysm. **B**, Dissected circle of Willis to show large aneurysm. **C**, Section through a saccular aneurysm showing the

### Morphology

**AVMs** involve vessels in the subarachnoid space extending into brain parenchyma. In macroscopic appearance, they resemble a tangled mass of dilated vascular channels (Fig. 23-11). Microscopically, they are enlarged blood vessels, some of which are often with evidence of prior hemorrhage. Some vessels can be recognized as arteries by the presence of fragmented internal elastic lamina, while others show marked thickening of the wall.

fragmented internal elastic lamina, while others show marked thickening or partial occlusion by hyalinized connective tissue.

**Cavernous hemangiomas** consist of distended, loosely organized vascular channels with thin walls; they are devoid of intervening nervous tissue (thus distinguishing them from arteriovenous malformations). They occur most often in the cerebellum, pons, and subcortical regions, and have frequent arteriovenous shunting. Foci of old hemorrhage, infarction, and calcification frequent in the walls of the vessels.

**Capillary telangiectasias** are microscopic foci of dilated, thin-walled vascular channels in the relatively normal brain parenchyma and occurring most frequently in the pons. **Venous angiomas** consist of aggregates of ectatic venous channels. These latter two types of vascular malformations are unlikely to bleed or cause symptoms, and are most commonly discovered as incidental findings.



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Figure 23-11 Arteriovenous malformation.

## Other Vascular Diseases

### Hypertensive Cerebrovascular Disease



The most important effects of hypertension on the brain include massive hypertensive intracerebral hemorrhages, lacunar infarcts, slit hemorrhages, and hypertensive encephalopathy. Over the past few decades, treatment of hypertension and more extensive screening for early disease, both of which have contributed to a decrease in the incidence of these complications. Nevertheless, these continue to be important diseases because of the access to health care.

Hypertension affects the deep penetrating arteries and arterioles that supply the basal ganglia and brain stem. Hypertension causes several changes, including hyaline arteriolar sclerosis in arterioles. These changes are weaker than are normal vessels and are more vulnerable to rupture. In some instances, with the development of minute aneurysms in vessels that are less than 300  $\mu\text{m}$  in diameter. These can rupture.

An important clinical and pathologic outcome of arteriolar sclerosis is the development of *lacunes*. Lacunar infarcts are just a few millimeters wide (<15 mm as an arbitrary definition). They are found most commonly in the basal ganglia and thalamus, internal capsule, deep white matter, and pons, and they consist of cavities lined by macrophages and surrounding gliosis. Depending on their location in the CNS, lacunes can either cause or result in neurologic impairment.

Hypertension also gives rise to rupture of the small-caliber penetrating vessels and the development of intracerebral hemorrhages. Hemorrhages resorb, leaving behind a slitlike cavity (*slit hemorrhage*) surrounded by brownish discoloration.

Acute hypertensive encephalopathy is a clinicopathologic syndrome characterized by diffuse cerebral edema, confusion, vomiting, and convulsions, sometimes leading to coma. Rapid therapeutic intervention to reduce intracranial pressure is required, since the syndrome does not usually remit spontaneously. Patients may show an edematous brain, with or without transtentorial or tonsillar herniation. Petechiae and areas of hemorrhage in the white matter may be seen microscopically.

#### Vasculitis

A variety of inflammatory processes that involve blood vessels may lead to luminal compromise. A small and large vessels was previously seen in association with syphilis and tuberculosis, but now with immunosuppression and opportunistic infection (such as toxoplasmosis, aspergillosis, and CMV). A form of vasculitis, such as polyarteritis nodosa, may involve cerebral vessels and cause single or multiple infarcts. *Angiitis of the CNS* is an inflammatory disorder that involves multiple small to medium-sized arteries. It is characterized by chronic inflammation, multinucleated giant cells (with or without granuloma formation). Affected individuals manifest a diffuse encephalopathic clinical picture, often with cognitive dysfunction and immunosuppressive treatment.

### SUMMARY

**Cerebrovascular Diseases** Stroke is the clinical term for a disease with acute focal deficit as the result of vascular lesions, either hemorrhage or loss of blood supply. It follows loss of blood supply and can be widespread, focal, or affect regions of vascular supply ("watershed" infarcts). Focal cerebral infarcts are most commonly the result of subsequent fragmentation of an embolism, a nonhemorrhagic infarct can be hemorrhagic. Primary intraparenchymal hemorrhages are typically due to either hypertension or angiopathy. Spontaneous subarachnoid hemorrhage is usually caused by an abnormality, such as an aneurysm or arteriovenous malformation.







## CENTRAL NERVOUS SYSTEM TRAUMA

Trauma to the brain and spinal cord is a significant cause of death and disability. Severity and site of outcome: injury of several cubic centimeters of brain parenchyma may be clinically silent (if in the spinal cord), or fatal (involving the brain stem).

The magnitude and distribution of traumatic brain lesions depend on the shape of the object causing impact, and whether the head is in motion at the time of injury. A blow to the head may be *penetrating*, *an open* or *a closed injury*. Severe brain damage can occur in the absence of external signs of head injury. Severe lacerations and even skull fractures do not necessarily indicate damage to the underlying brain. In spinal fractures, trauma can cause parenchymal injury and vascular injury; combinations are common.

### Traumatic Parenchymal Injuries

When there is impact of an object with the head, injury may occur from collision of the brain with the skull (a *coup* injury) or on the opposite side (*contrecoup*). Both coup and contrecoup lesions are comparable gross and microscopic appearances. A contusion is caused by rapid tissue displacement, tearing of blood vessels, and subsequent hemorrhage, tissue injury, and edema. Since they are the points of impact, they are the most susceptible, whereas cerebral cortex along the sulci is less vulnerable. The most common locations correspond to the most frequent sites of direct impact and to regions of the brain that overlie a rough surface, such as the frontal lobes along the orbital gyri and the temporal lobes. If there is penetrating trauma, such as a bullet or a skull fragment from a fracture, a *laceration* occurs, with tissue tearing, hemorrhage, and injury along a linear path.

#### Morphology

Contusions, when seen on cross-section, are wedge shaped, with the broad base at the surface and centered on the point of impact (Fig. 23-12A). The histologic appearance of contusions is independent of the type of trauma. In the earliest stages there is edema and hemorrhage. During the next few hours, blood extravasates throughout the involved area across the width of the cerebral cortex, and into the white matter and subarachnoid space. Although functional effects are seen earlier, morphologic evidence of injury in the neocortex (pyknosis of nucleus, eosinophilia of the cytoplasm, disintegration of cell) takes hours to appear. The inflammatory response to the injured tissue follows its usual course, with neutrophils preceding the appearance of macrophages. In contrast to ischemic lesions, the superficial layer of cortex may be preserved and gliotic, trauma affects the superficial layers most severely.

Old traumatic lesions have a characteristic macroscopic appearance: they are depressed, retracted, yellowish brown patches involving the crests of gyri (Fig. 23-12B). More extensive hemorrhagic regions of brain trauma give rise to larger cavitated lesions, which can resemble remote infarcts. In sites of old contusions, gliosis and residual hemosiderin-laden macrophages predominate.

Although injury to the surface of the brain is often the most dramatic, widespread injury to axons (*diffuse axonal injury*) can be even more devastating. The movement of one region of brain relative to another can lead to the disruption of axonal integrity and function. Angular acceleration alone, in the absence of focal lesions, can cause axonal injury as well as hemorrhage. As many as 50% of patients who develop coma shortly after cerebral contusions, are believed to have white matter damage and diffuse axonal injury. Although widespread, lesions are most commonly found near the angles of the lateral ventricles and in the

Diffuse axonal injury is characterized by the wide but often asymmetric distribution of axonal swelling. It begins within hours of the injury and may persist for much longer. These are best demonstrated with silver stain or immunohistochemistry for proteins within axons.

*Concussion* describes reversible altered consciousness from head injury in the absence of contus. transient neurologic dysfunction includes loss of consciousness, temporary respiratory arrest, and neurologic recovery is complete, amnesia for the event persists. The pathogenesis of the sudden activity is unknown.

### **Traumatic Vascular Injury**

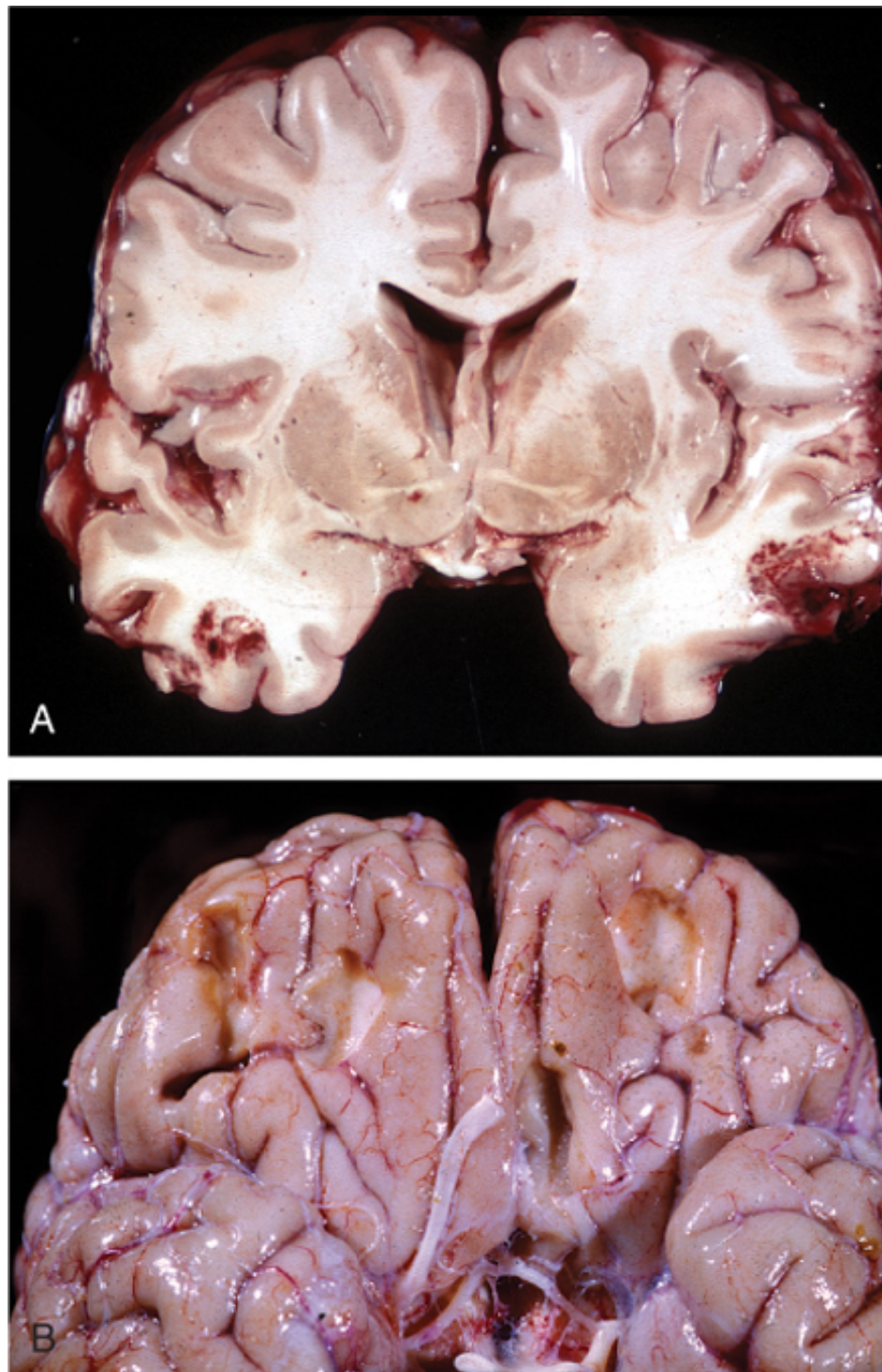


Figure 23-12 Cerebral trauma. **A**, Acute contusions are present in both temporal lobes, with areas of hemorrhage and edema. **B**, Chronic contusions are present on the inferior frontal surface of this brain, with a yellow color (associated with the breakdown of blood products).

Vascular injury is a frequent component of CNS trauma and results from direct trauma and disruption of blood vessels, leading to hemorrhage. Depending on which vessels rupture, hemorrhage may occur in any of several locations (sometimes in combination): *epidural*, *subdural*, *subarachnoid*, and *intraparenchymal* (Fig. 23-13A). Intraparenchymal hemorrhages most often occur at sites of contusions and lacerations.

### **Epidural Hematoma**

The dura is normally tightly applied to the inside of the skull, fused with the periosteum. Vessels that are important, the middle meningeal artery, are vulnerable to injury, particularly with skull fractures. If the skull is deformable, a temporary displacement of the skull bones may tear a vessel in the absence of a fracture. If a vessel has been torn, the accumulation of blood under arterial pressure can cause separation of the dura from the surface of the skull (Fig. 23-13B). The expanding hematoma has a smooth inner contour that corresponds to the surface of the skull. *Clinically, patients can be lucid for several hours between the moment of trauma and the development of symptoms.* An epidural hematoma may expand rapidly and is a neurosurgical emergency requiring prompt drainage.

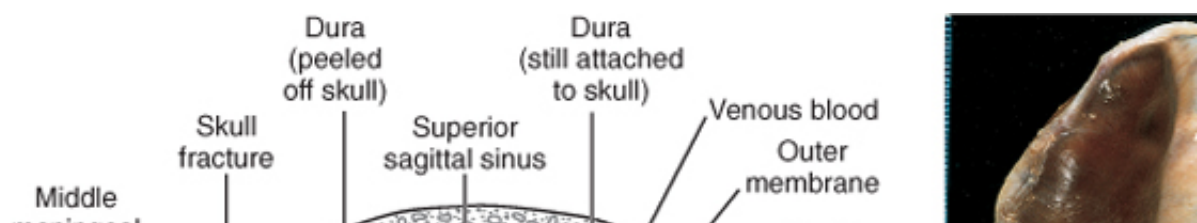
### **Subdural Hematoma**

The rapid movement of the brain that occurs in trauma can tear the bridging veins that extend from the cerebral hemispheres through the subarachnoid and subdural space to empty into dural sinuses. These veins are prone to tearing, and their disruption leads to bleeding into the subdural space. In elderly patients, the bridging veins are stretched out and the brain has additional space for movement, accounting for the occurrence of subdural hematomas in these patients, even after relatively minor head trauma. Infants are also susceptible because their bridging veins are thin-walled.

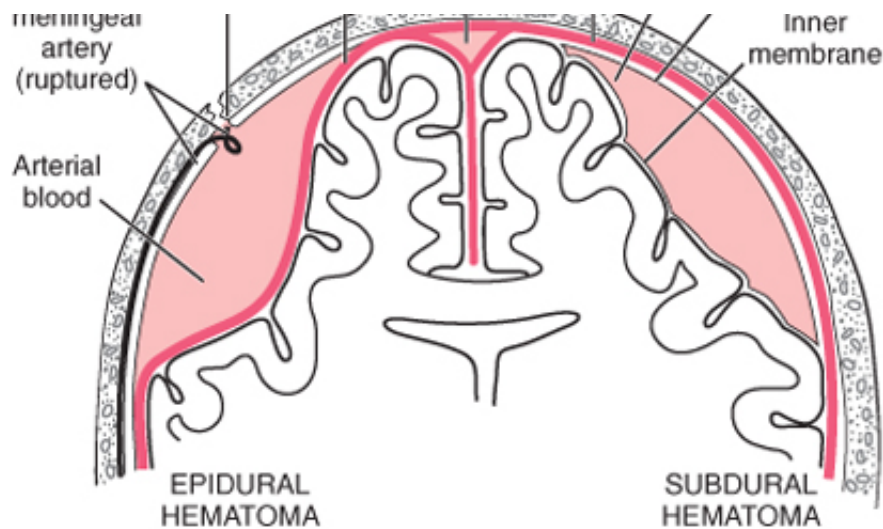
Subdural hematomas most often become manifest within the first 48 hours after injury. They are typically crescentic in lateral aspects of the cerebral hemispheres and are bilateral in about 10% of cases. Neurologic signs are due to the pressure exerted on the adjacent brain. These may be focal, but often the clinical manifestations include headache or confusion. In time there may be slowly progressive neurologic deterioration, and eventually, decompensation.

### **Morphology**

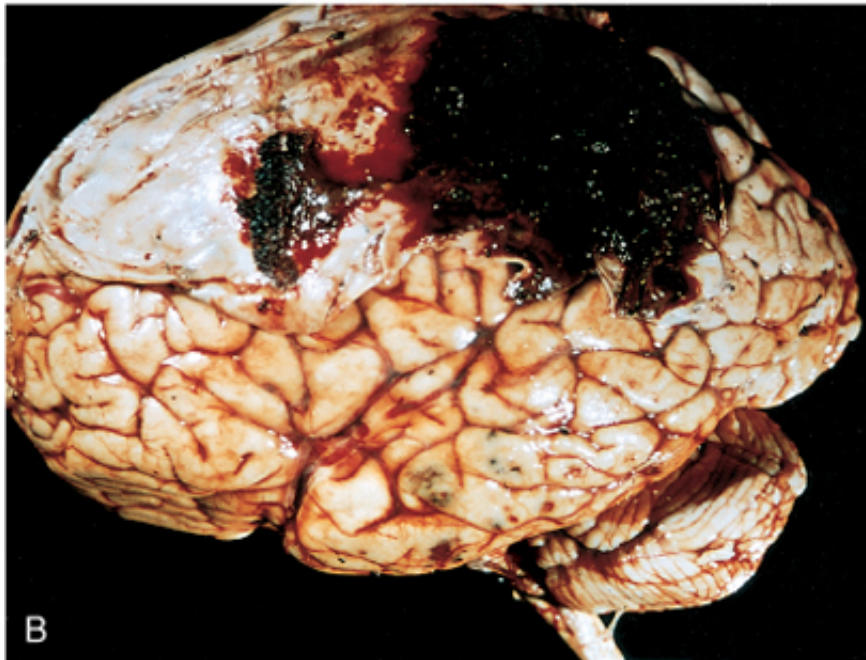
On macroscopic examination the acute subdural hematoma appears as a collection of clotted blood apposed along the contour of the brain surface, without extension into sulci (Fig. 23-13C). The underlying brain is flattened, and the subarachnoid space is compressed. Typically, venous bleeding is self-limited; breakdown and organization of the hematoma take place over time. Subdural hematomas organize by lysis of the clot (about 1 week), growth of fibroblasts from the dural surface into the hematoma (2 weeks), and early development of hyalinized connective tissue (1-3 months). Organized hematomas are attached to the surface of the dura and are not adherent to the underlying arachnoid. The lesion can retract as the granulation tissue matures, until there is only a thin layer of reactive connective tissue ("subdural membranes"). Subdural hematomas commonly rebleed (**chronic subdural hematomas**), presumably from the thin-walled vessels of the granulation tissue, leading to a variety of microscopic findings consistent with a variety of ages. The treatment of symptomatic subdural hematomas is to remove the organized blood and associated organizing tissue.



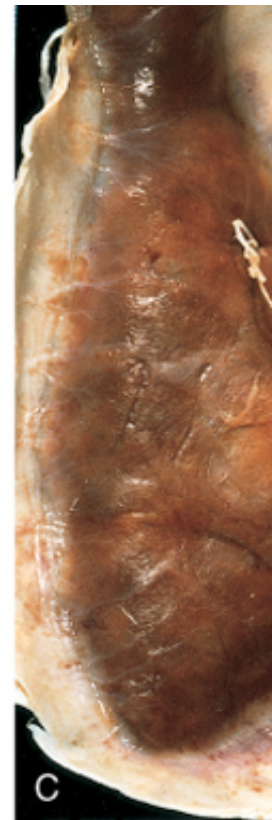




A



B



C

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Figure 23-13 Traumatic intracranial hemorrhages. **A**, Epidural hematoma (*left*) in which rupture of a meningeal artery and skull fracture, leads to accumulation of arterial blood between the dura and the skull. In a subdural hematoma (*right*) between the brain and the superior sagittal sinus leads to the accumulation of blood between the dura and the arachnoid covering a portion of the dura. **C**, Large organizing subdural hematoma attached to the dura. (**B**, Courtesy of Massachusetts General Hospital, Boston, Massachusetts.)

## SUMMARY

**Traumatic Parenchymal Injury** Physical injury to the brain can occur when the skull comes into forceful contact with the brain. If the head is able to move, there can be contact between the skull and brain, both at the original point of contact (coup injury) and on the opposite side where the brain eventually hits the skull as it moves with the skull (contrecoup injury). Rapid displacement of the head and brain can lead to tearing of axons (diffuse axonal injury), which often causes immediate onset of severe and irreversible neurologic deficits. Tearing of blood vessels associated with trauma can lead to accumulation of blood in any of three spaces: epidural hematoma, subdural hematoma, or subarachnoid hemorrhage.





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## CONGENITAL MALFORMATIONS AND PERINATAL BRAIN INJURY

The incidence of CNS malformations, giving rise to mental retardation, cerebral palsy, or neural tube defects, is about 1 in 1000 live births. Malformations of the brain are more common in the setting of multiple birth defects. Prenatal or perinatal injury to the developing CNS can result in tissue destruction. Because different parts of the brain develop at different times (and afterwards), the timing of an injury will be reflected in the pattern of malformation. Although the exact mechanisms of many malformations remain unknown, both genetic and environmental factors are clearly at play. Mutations affecting neuronal and glial development, migration, and connection can cause CNS malformation. Additionally, infectious agents are known to have teratogenic effects.

### Malformations

#### Neural Tube Defects

Among the earliest stages in brain development is the formation of the neural tube, the inside of which will become the brain and spinal cord. Failure of a portion of the neural tube to close properly, may lead to one of several malformations. All are characterized by abnormalities involving the meninges, and overlying bone or soft tissues. Collectively, neural tube defects are the most frequent type of congenital malformation.

Folate deficiency during the initial weeks of gestation is a risk factor; prenatal vitamins are aimed at preventing this. A combination of ultrasound and maternal screening for elevated  $\alpha$ -fetoprotein has increased the early detection of neural tube defects. The overall recurrence risk in subsequent pregnancies is 4% to 5%.

The most common neural tube defects involve the spinal cord. These can range from asymptomatic spina bifida to severe malformation with a flattened, disorganized segment of spinal cord, associated with an overlying skin lesion.

*Myelomeningocele* is an extension of CNS tissue through a defect in the vertebral column (Fig. 23-1). It is the most common neural tube defect, occurring in the lumbosacral region; patients have motor and sensory deficits in the lower extremities and problems with bladder and bowel control. Symptoms derive from the abnormal spinal cord in this region, and are often compounded by infection and overlying skin lesions.





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Figure 23-14 Myelomeningocele. These defects occur because the caudal neural tube fails to close properly. In m cord parenchyma are included in the cystlike structure visible just above the buttocks. Because such lesions expos a common complication.

At the other end of the developing brain, *anencephaly* is a malformation of the anterior end of the and top of skull. An *encephalocele* is a diverticulum of malformed CNS tissue extending through a involves the occipital region or the posterior fossa. When it occurs anteriorly, brain tissue can exte Forebrain Malformations

The volume of brain may be abnormally large (*megalecephaly*) or small (*microencephaly*). Micro the two, is usually associated with a small head as well (microcephaly). It can occur in a wide rang chromosome abnormalities, fetal alcohol syndrome, and human immunodeficiency virus 1 (HIV-1) are associated with a decreased number of neurons destined for the cerebral cortex. Disruption o differentiation during development can lead to a disruption of the normal gyration and six-layered (*agyria*) or, in case of more patchy involvement, *pachygyria* is characterized by an absence of nor brain. The cortex is abnormally thickened and is usually only four-layered. Single-gene defects ha lissencephaly. *Polymicrogyria* is characterized by an increased number of irregularly formed gyri t cobblestone-like surface. These changes can be focal or widespread. The normal cortical architec adjacent gyri often show fusion of the superficial molecular layer. *Holoprosencephaly* is characteri patterning. Mild forms may just show absence of the olfactory bulbs and related structures (arrhin not divided into hemispheres or lobes. The severe forms may be associated with facial midline de well as polymicrogyria can be the result of acquired or genetically determined disruption of norma defects including mutations in sonic hedgehog have been linked to holoprosencephaly.

#### Posterior Fossa Anomalies

The most common malformations in this region of the brain result in either misplaced or absent ce with hydrocephalus.

The *Arnold-Chiari malformation* (Chiari type II malformation) consists of a small posterior fossa ar downward extension of *vermis* through the foramen magnum; hydrocephalus and a lumbar myelo the *Chiari I malformation*. low-lying cerebellar tonsils extend through the foramen magnum at the l

obstruction of CSF flow and compression of the medulla, resulting in symptoms of headache or cranial nerve deficits. Decompression of the posterior fossa through a foramen magnum decompression can alleviate the symptoms.

Unlike Chiari malformation, the *Dandy-Walker malformation* is characterized by an enlarged posterior horn of the lateral ventricle, which is absent, or present only in rudimentary form in its anterior portion. In its place is a large midline cyst contiguous with leptomeninges on its outer surface. Dysplasias of brainstem nuclei are commonly associated with this malformation.

### Spinal Cord Abnormalities

In addition to neural tube defects, structural alterations inside the spinal cord (and not associated with overlying skin) can occur. These lesions are characterized by a discontinuous or confluent expansion of the cord (*hydromyelia*) or by formation of a fluid-filled cleft-like cavity in the inner portion of the cord (*syringomyelia*). These lesions also develop as an acquired lesion during life secondary to alterations in CSF flow by tumor or trauma, or destruction of the adjacent gray and white matter and are surrounded by a dense feltwork of reactive gliosis. The gray matter is most often affected.

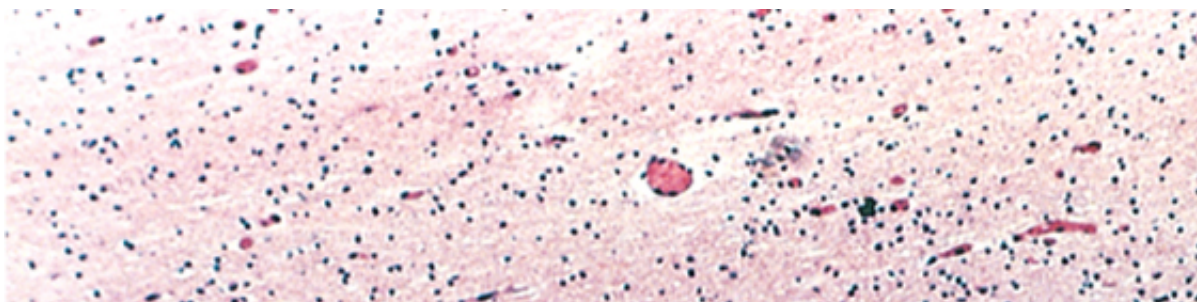
### Perinatal Brain Injury

A variety of exogenous factors can injure the developing brain. Injuries that occur early in gestation, often evoking the usual "reactive" changes in the parenchyma and therefore may be difficult to distinguish from those occurring in the perinatal period is an important cause of childhood neurologic disability. *Cerebral palsy* is a group of neurologic motor deficits characterized by spasticity, dystonia, ataxia/athetosis, and paresis attributable to prenatal and perinatal periods. Signs and symptoms may not be apparent at birth and declare themselves as the child proceeds.

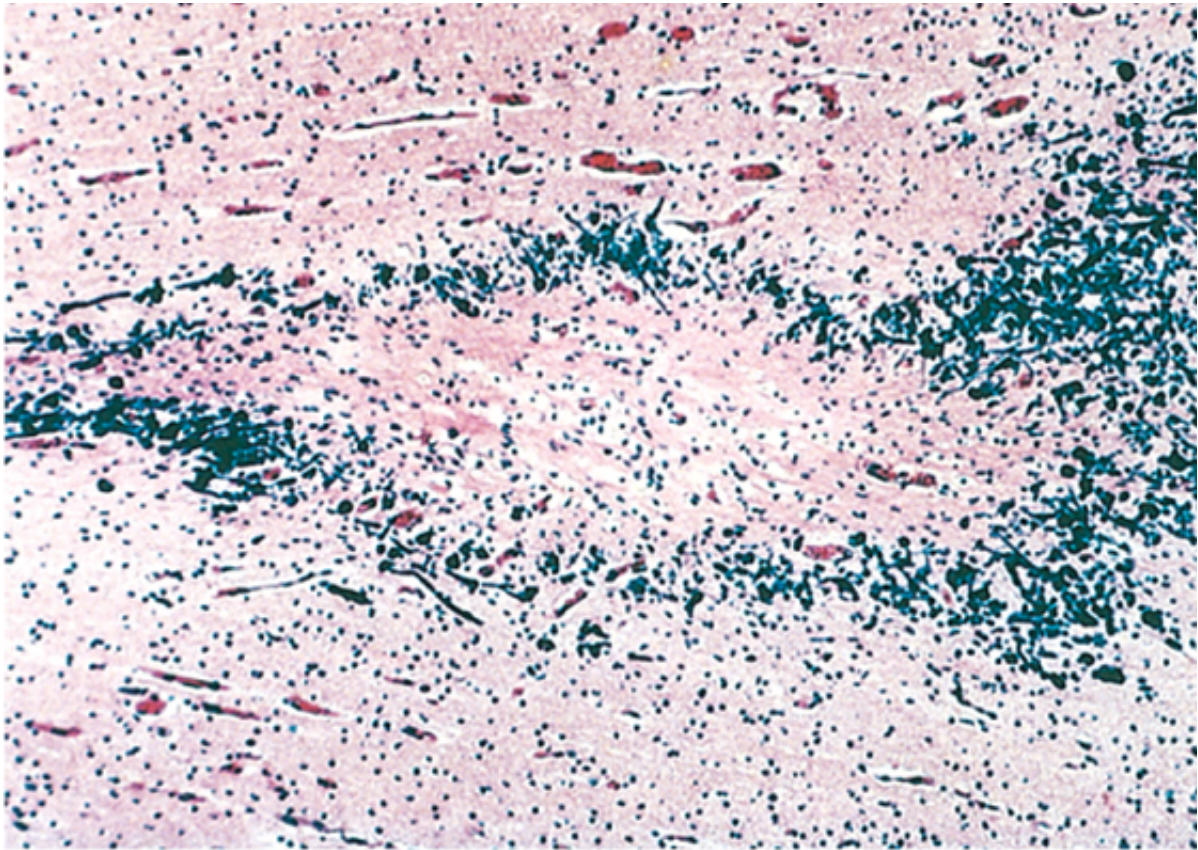
Two major types of injury occur in the perinatal period: hemorrhages and/or infarcts. These are difficult to distinguish in adults because of their locations and the types of reaction in the surrounding tissue. In premature infants, an *intraparenchymal hemorrhage* within the germinal matrix, near the junction between the thalamus and the brainstem, may extend into the ventricular system and thence to the subarachnoid space, sometimes leading to the supratentorial periventricular white matter (*periventricular leukomalacia*), especially in premature infants. These are chalky yellow plaques consisting of discrete regions of white matter necrosis and mineralization. In older children and adults, large cystic lesions can develop throughout the hemispheres; this is called *encephalopathy*.

### SUMMARY

**Congenital Malformations and Perinatal Brain Injury** Malformations of the brain can be caused by a variety of genetic factors or external insults. The timing of the injury will determine the type of malformation. The timing of the injury will determine the type of malformation based on the type of developmental processes occurring at the point of injury. Malformations of the brain include alterations in the closure of the neural tube, proper folding of portions of the neural tissue, and migration of neurons to the appropriate location. Perinatal brain injury mostly takes one of two forms: either hemorrhage, often in the region of the germinal matrix, or ischemic lesions, leading to periventricular leukomalacia.







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Figure 23-15 Perinatal brain injury. Periventricular leukomalacia: central focus of white matter necrosis with a pale rim (staining *blue*).



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## INFECTIONS OF THE NERVOUS SYSTEM

The brain and its coverings, as with all other parts of the body, can be affected by infections. Some have an absolute predilection for the nervous system (such as rabies), while others can affect many other parts of the body (*Staphylococcus aureus* and other bacteria). Damage to nervous tissue may be the consequence of a direct infectious agent, or it may occur indirectly through the elaboration of microbial toxins, the destruction of normal tissue, or the influence of immune-mediated mechanisms.

An infectious agent must use one of several different possible routes of entry to cause disease in the central nervous system.

**Hematogenous spread** via the arterial blood supply is the most common means of entry. The spread, through the anastomoses between veins of the face and the venous sinuses of the head, of microorganisms is almost invariably post-traumatic, with introduction of foreign material. It may also occur if microbes are introduced with a lumbar puncture needle. **Local extension** from an established focus of infection. The infection may originate in an air sinus, most often the mastoid or frontal; from an infected focus in the cranium or spine causing osteomyelitis, bone erosion, and propagation of the infection into the meninges; or from a malformation, such as meningomyelocele. **Peripheral nerves** can also serve as the path of entry for certain viruses, such as rabies and herpes zoster.

### Epidural and Subdural Infections

These spaces can be involved with bacterial or fungal infections, usually as a consequence of direct extension from a focus of infection commonly associated with osteomyelitis, arises from an adjacent focus of infection, such as sinusitis. If the process occurs in the spinal epidural space, it may cause spinal cord compression and constitute a surgical emergency. The infection of the skull or air sinuses may also spread to the subdural space, producing subdural empyema. The meninges are usually unaffected, but a large subdural empyema may produce a mass effect. In addition, it may bridge veins that cross the subdural space, resulting in venous occlusion and infarction of the brain. The source of the infection. Most patients are febrile, with headache and neck stiffness, and if untreated, lethargy, and coma. With treatment, including surgical drainage, resolution of the empyema is complete, a thickened dura may be the only residual finding. With prompt treatment, complete resolution is possible.

### Meningitis

**Meningitis** is an inflammatory process of the leptomeninges and CSF within the subarachnoid space. It may be caused by a spread of the infection from the meninges into the underlying brain. Meningitis is usually caused by bacteria, but it may also occur in response to a nonbacterial irritant introduced into the subarachnoid space. Infectious agents may be *acute pyogenic* (usually bacterial), *aseptic* (usually viral), and *chronic* (usually tuberculous, spirochetal, or fungal). Characteristics of inflammatory exudate on CSF examination and the clinical evolution of the illness are helpful in diagnosis.

#### **Acute Pyogenic Meningitis (Bacterial Meningitis)**

While a wide range of bacteria can cause acute pyogenic meningitis, there is a relationship between the causative organisms and the age of the patient. In neonates, common organisms are *Escherichia coli* and the group B streptococcus. In infants, *Streptococcus pneumoniae* and *Listeria monocytogenes* are more common. Among adolescents and adults, *S. pneumoniae* is the most common pathogen, with occasional clusters of cases representing public health problems. In patients typically show systemic signs of infection superimposed on clinical evidence of meningeal irritation including headache, photophobia, irritability, clouding of consciousness, and neck stiffness. CSF examination shows increased pressure, abundant neutrophils, elevated protein, and reduced glucose. Bacteria may be seen on Gram stain. Sometimes a few hours before the neutrophils appear. If untreated, pyogenic meningitis can be fatal. The use of antibiotics has markedly reduced the mortality.

### Morphology

In acute meningitis, an exudate is evident within the leptomeninges over the surface (Fig. 23-16A). The meningeal vessels are engorged and prominent. From the areas of greatest concentration of pus can be followed along blood vessels on the brain surface. When the meningeal inflammatory cells infiltrate the walls of the leptomeningeal veins and may spread into the brain (focal cerebritis), or the inflammation may extend to the ventricles, producing meningitis. On microscopic examination, neutrophils fill the entire subarachnoid space in severely affected areas, predominantly around the leptomeningeal blood vessels in less severe cases. Gram stain reveals varying numbers of the causative organism. Bacterial meningitis can lead to abscesses in the brain (Fig. 23-16B), discussed later. Phlebitis may also lead to hemorrhagic infarction of the underlying brain. If treated early, there may be little residual damage after it resolves.

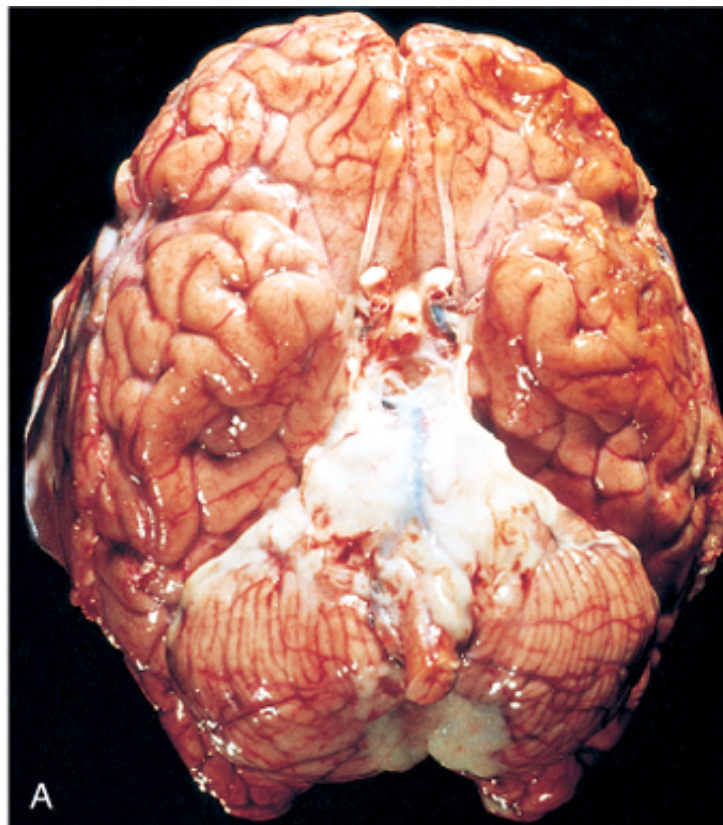
### ***Aseptic Meningitis (Viral Meningitis)***

Aseptic meningitis is a misnomer; it is a clinical term for an illness comprising meningeal irritation, of relatively acute onset without recognizable organisms. The clinical course is less fulminant than bacterial meningitis, and most often is treated symptomatically. The CSF shows an increased number of lymphocytes, protein elevation is only moderate, and glucose content is nearly always normal. In approximately 70% of cases, an agent is identified, most commonly an enterovirus. There are no distinctive macroscopic characteristics except in severe instances. On microscopic examination, there is either no recognizable abnormality or a mild to moderate inflammation with lymphocytes.

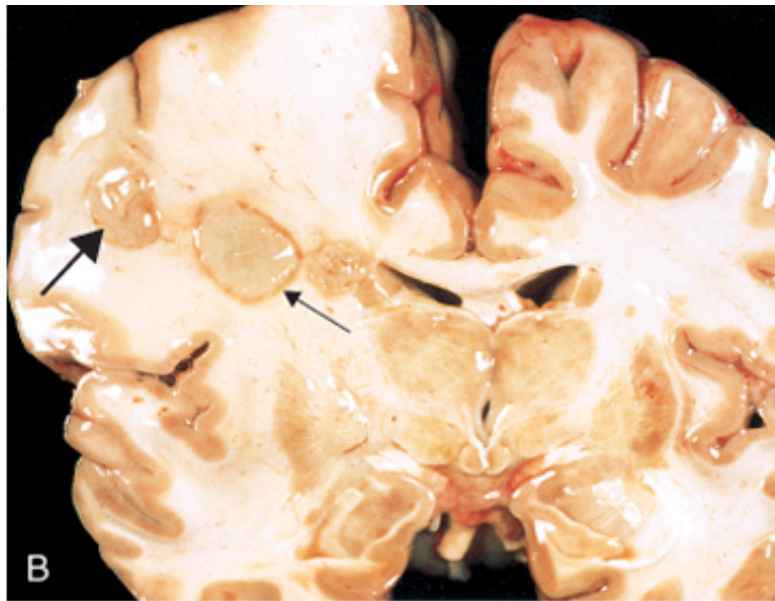
### ***Chronic Meningitis***

Several pathogens, including mycobacteria and some spirochetes, are associated with chronic meningitis. The disease may also be a parenchymal component of the disease.

Tuberculous Meningitis







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 Figure 23-16 Bacterial infections. **A**, Pyogenic meningitis. A thick layer of suppurative exudate covers the brain. **B**, Cerebral abscesses in the frontal white matter (arrows). (**A**, From Golden JA, Louis DN: Images in Clinical Medicine, 2nd ed. Philadelphia, PA, 1994. Copyright © 1994 Massachusetts Medical Society. All rights reserved.)

Tuberculous meningitis usually presents with generalized symptoms of headache, malaise, mental status changes, and a moderate increase in cellularity of the CSF (pleiocytosis) made up of mononuclear cells, or a mixed population of mononuclear cells; the protein level is elevated, often strikingly so, and the glucose content typically low. Infection with *Mycobacterium tuberculosis* may also result in a well-circumscribed intraparenchymal abscess associated with meningitis. Chronic tuberculous meningitis is a cause of arachnoid fibrosis, which

### Morphology

The subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain, obliterating the cisterns and encasing cranial nerves. There may be discrete white plaques on the surface of the leptomeninges. Arteries running through the subarachnoid space may show obliterative endarteritis with inflammatory infiltrates in their walls and marked intimal thickening. The infection spreads from the CSF to the choroid plexuses and ependymal surface. On microscopic examination, the infiltrate consists of lymphocytes, plasma cells, and macrophages. Florid cases show well-formed granulomas with caseous necrosis and giant cells, similar to the lesions of tuberculosis elsewhere in the body.

### Neurosyphilis

Neurosyphilis is a tertiary stage of syphilis and occurs in only about 10% of individuals with untreated syphilis. The most common manifestation is meningeal, called meningovascular neurosyphilis. As with other chronic infections, the CSF shows a pleocytosis. *Paretic neurosyphilis* is caused by invasion of the brain by *Treponema pallidum* and manifests itself with mental and physical functions with mood alterations (including delusions of grandeur), terminating in dementia. Another form of neurosyphilis, resulting from damage to the sensory nerves in the dorsal roots produces sensory ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot's joints); and absence of deep tendon reflexes. Individuals with neurosyphilis, and the rate of progression and severity of the disease seem to be accelerated. The disease may also be associated with infection, acute syphilitic meningitis, or meningovascular syphilis; direct parenchymal invasion of the brain.

### Morphology

**Meningovascular neurosyphilis** is a chronic meningitis usually involving the base of the brain, but sometimes the cerebral convexities and the spinal leptomeninges. As with tuberculous meningitis, there is an associated obliterative endarteritis, but in this situation it has a distinctive perivascular reaction rich in plasma cells and lymphocytes. Cerebral gummas (mass lesions of the brain) are also seen in some cases.



reaction rich in plasma cells and lymphocytes. **Cerebral gummas** (mass lesions) also occur in relation to meninges and extend into the brain. When **paretic neurosyphilis** causes parenchymal damage particularly in the frontal lobe, characterized by loss of neurons, microglia (rod cells) and gliosis. The spirochetes can rarely be demonstrated in tissue. In **tabes dorsalis** consist of loss of both axons and myelin in the dorsal roots, with dorsal columns of the spinal cord.

*Neuroborreliosis* represents involvement of the nervous system by the spirochete *Borrelia burgdorferi*. Neurologic symptoms are highly variable and include aseptic meningitis, facial nerve palsies, mild

### **Parenchymal Infections**

The entire gamut of microbial organisms (virus to parasites) can potentially infect the brain. The different patterns of involvement, although the distinctions are not absolute. In general, viral infections produce the most localized, and other organisms generally produce more widespread involvement with any agent is typical.

### **Brain Abscesses**

Brain abscesses are nearly always caused by bacterial infections; these can arise by direct implantation of adjacent foci (mastoiditis, paranasal sinusitis), or hematogenous spread (usually from a primary site after tooth extraction). Predisposing conditions include acute bacterial endocarditis, which tends to be associated with congenital heart disease, in which there is a right-to-left shunt and loss of pulmonary filtration of organisms as in bronchiectasis.

Abscesses are destructive lesions, and patients almost invariably present clinically with progressive signs of raised intracranial pressure. The CSF white cell count and protein level are raised, but the source of infection may be apparent, or a small systemic focus may have ceased to be symptomatic. Pressure and progressive herniation can be fatal, and abscess rupture can lead to ventriculitis, meningitis. With surgery and antibiotics, the otherwise high mortality rate can be reduced, with earlier intervention.

#### **Morphology**

Abscesses are discrete lesions with central liquefactive necrosis and a surrounding capsule (Fig. 16B). On microscopic examination, there is exuberant neovascularization around the abscess, responsible for the marked edema and formation of granulation tissue. Outside the capsule is a zone of reactive gliosis.

### **Viral Encephalitis**

Viral encephalitis is a parenchymal infection of the brain that is almost invariably associated with a more severe, better termed *meningoencephalitis*. While different viruses may show varying patterns of injury, there are perivascular and parenchymal mononuclear cell infiltrates, microglial nodules, and neuronophagia. Some may form inclusion bodies.

The nervous system is particularly susceptible to viruses such as rabies and polio. Some viruses infect the entire CNS, while others preferentially involve particular areas of the brain (such as medial temporal lobes, limbic system). In addition to direct infection of the nervous system, the CNS can also be injured by immune mechanisms. Intrauterine viral infection may cause *congenital malformations*, as occurs with rubella.

#### **Arboviruses**

Arboviruses (arthropod-borne viruses) are an important cause of epidemic encephalitis, especially those capable of causing serious morbidity and high mortality. Among the more commonly encountered are Japanese encephalitis and West Nile virus. Animal hosts act as disease reservoirs for the arboviruses, which are transmitted to humans by mosquitoes. Patients develop generalized neurologic symptoms, such as seizures, confusion, delirium, and stupor, as well as reflex asymmetry and ocular palsies. The CSF is usually colorless but with a slightly elevated protein and pleiocytosis that rapidly converts to lymphocytes; the protein level is elevated, but sugar content is normal.

### **Morphology**

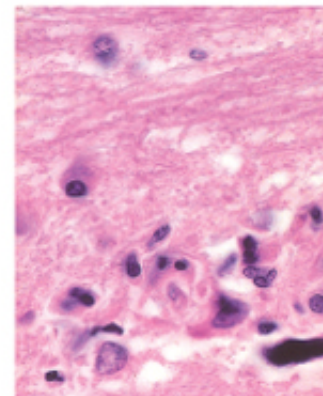
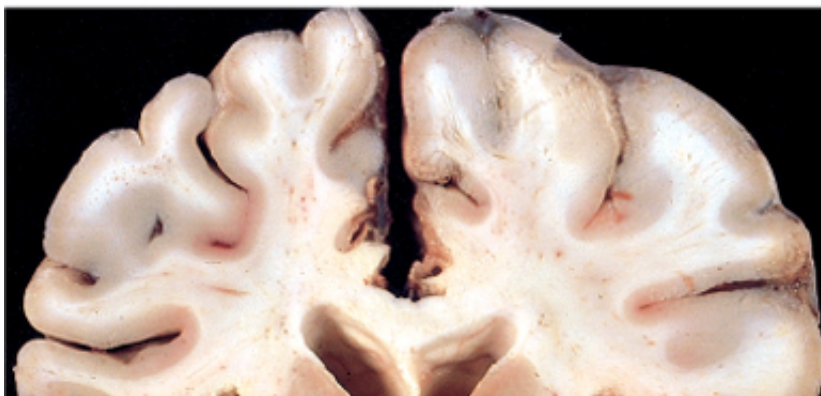
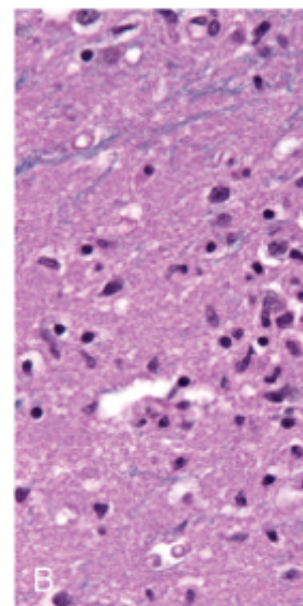
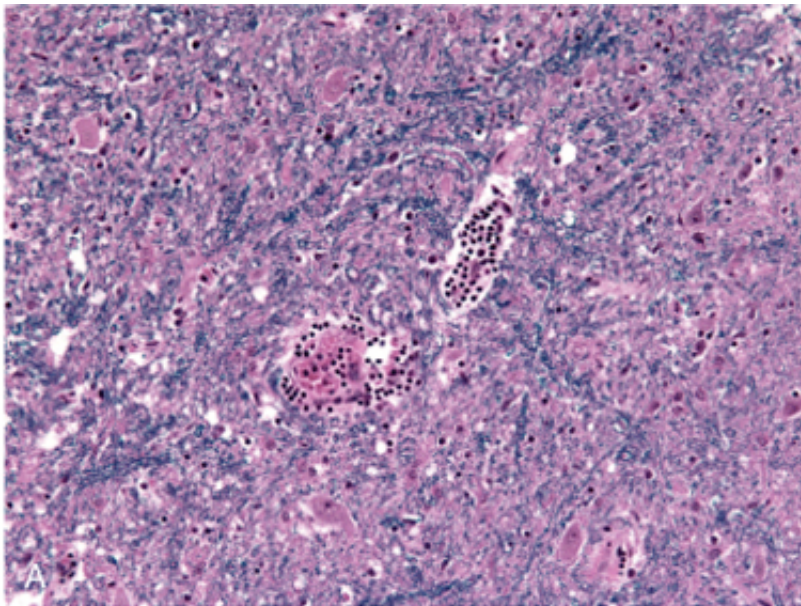
Although the various arbovirus encephalitides differ in epidemiology and prognosis picture is similar albeit of differing severity and extent. Characteristically, there is a meningoencephalitis (sometimes with neutrophils) with a typically perivascular distribution. Multifocal gray and white matter necrosis is seen; there is evidence of individual neuron phagocytosis of the debris, termed neuronophagia; localized collections of microglial nodules, are often present (Fig. 23-17B). In severe cases there may be a necrotizing associated focal hemorrhages.

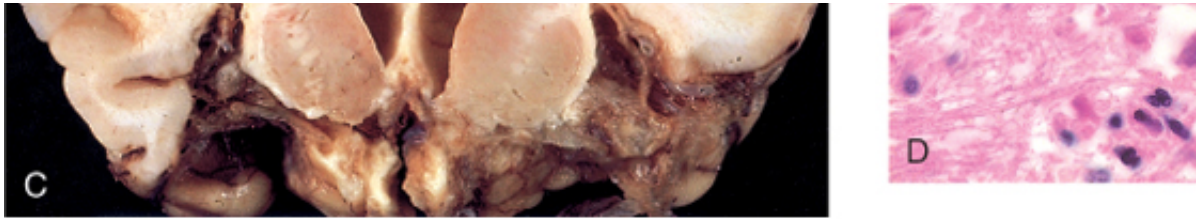
### **Herpes Simplex Virus Type 1**

Herpes simplex virus (HSV) type 1 produces an encephalitis that occurs in any age group but is rare in adults. Only some patients have prior oral herpetic lesions. The most common presenting symptom is personality change, reflecting the involvement of frontal and temporal lobes.

### **Morphology**

Herpes encephalitis starts in, and most severely involves, the inferior and medial temporal lobes and the orbital gyri of the frontal lobes (Fig. 23-17C). The infection is necrotizing in the most severely affected regions. Perivascular inflammatory infiltrates are usually present. Type A intranuclear viral inclusion bodies can be found in both neurons and glia.





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Figure 23-17 Viral infections. Characteristic findings of viral meningitis include perivascular cuffs of lymphocytes. In viral encephalitis, there is extensive destruction of inferior frontal and anterior temporal lobes. **D**, HIV encephalitis. Not a multinucleated giant cell. (**C**, Courtesy of Dr. T.W. Smith, University of Massachusetts Medical School)

## Herpes Simplex Virus Type 2

HSV-2 also affects the nervous system and usually manifests in adults as a meningitis. Disseminated infection occurs in neonates born by vaginal delivery to women with active primary HSV genital infections. The depth of the infection is acquired during passage through the birth canal rather than transplacentally.

## Varicella-Zoster Virus (Herpes Zoster)

Varicella-zoster virus (VZV) causes chickenpox during its primary infection, usually without any evidence of disease. The virus establishes latent infection in neurons of dorsal root ganglia. Reactivation in adults manifests as shingles, the distribution of one or a few dermatomes (*shingles*). This is usually a self-limited process, but there is often pain in the affected region (*post-herpetic neuralgia*).

VZV may cause a granulomatous arteritis, which may cause infarcts. In immunosuppressed patients, reactivation occurs. Inclusion bodies can be found in glia and neurons.

## Cytomegalovirus

CMV infects the nervous system in fetuses and immunosuppressed individuals. The outcome of infection in the fetus is that it produces severe brain destruction followed later by microcephaly with periventricular calcifications. In immunosuppressed individuals with acquired immunodeficiency syndrome (AIDS), CMV is a common pathogen.

### Morphology

The most common pattern of involvement in the immunosuppressed patient is that of periventricular and subependymal disease, associated with CMV inclusion-bearing cells. Although any type of cell (neurons, glia, ependyma, endothelium) can be infected by CMV, there is a tendency for the infection to involve the paraventricular subependymal regions of the brain. This results in a severe hemorrhagic periventriculoencephalitis and choroid plexitis.

## Poliovirus

Poliovirus is an enterovirus that causes paralytic poliomyelitis. Although it has been eradicated by vaccination, there are still many regions where it remains a problem. Infection with poliovirus most often causes a mild illness, but in a small fraction of cases it secondarily invades the nervous system and damages motor neurons in the spinal cord. Of motor neurons, it produces a flaccid paralysis with muscle wasting and hyporeflexia in the affected segments. In the severe disease, death can occur from paralysis of respiratory muscles. *Post-polio syndrome* is a poorly understood condition associated with decreased muscle bulk and pain, typically developing 25 to 35 years after the resolution of the acute disease.

## Rabies

Rabies is a severe encephalitis transmitted to humans by the bite of a rabid animal; various animals can transmit the disease. Exposure to some species of bat, even without a bite, is also a risk factor for developing infection. The virus travels along the peripheral nerves from the wound site, so the incubation period depends on the distance from the site of exposure to the brain, usually taking a few months. The disease manifests initially with nonspecific symptoms of malaise and fever. As the disease advances, the patient shows extraordinary CNS excitability; the slightest touch is painful, with violent convulsions. Contracture of the pharyngeal musculature may create an aversion to swallowing even though the patient is thirsty. Alternating mania and stupor progress to coma and death from respiratory center failure.

## Human Immunodeficiency Virus

HIV can have direct effects on the nervous system as well as setting the stage for opportunistic infections of the nervous system (Table 23-1). As many as 60% of individuals with AIDS develop neurologic dysfunction, it dominates the clinical picture. Patterns of direct injury to the brain include:

*Aseptic HIV-1 meningitis* occurring within 1 to 2 weeks of seroconversion in about 10% of patients. It is characterized by lymphocytic meningitis, perivascular inflammation, and some myelin loss in the hemisphere. *HIV-1 encephalitis* causing AIDS-dementia complex. This dementia begins insidiously with mental status changes, such as apathy and depression. The brains of individuals with HIV-1 encephalitis contain widely distributed infiltrates of microglial nodules containing macrophage-derived multinucleated giant cells. It is thought that neuronal injury follows the secretion of cytokines and chemokines from HIV-infected macrophages. *Vacuolar myelopathy* involving the tracts of the spinal cord can resemble subacute combined degeneration. Levels of vitamin B<sub>12</sub> are normal. The pathogenesis of the lesion is unknown; it does not appear that HIV virus is not present within the lesions.

**Table 23-1. Primary HIV-Associated Neurologic Disorders**

<b>Central Nervous System</b>
Primary HIV encephalopathies
Multinucleate giant-cell encephalitis (HIV encephalitis)
HIV-associated white matter disease (HIV leukoencephalopathy)
Neocortical/gray matter disease (HIV poliodystrophy)
Mixed patterns
Vacuolar myelopathy
Lymphocytic meningitis
Acute, monophasic meningitis
Chronic aseptic meningitis
Cerebral vasculitis
<b>Peripheral Nervous System</b>
Distal symmetric polyneuropathy
Inflammatory demyelinating neuropathies
Spinal and cranial radiculitis
Vasculitic neuropathy
<b>Skeletal Muscle</b>
Inflammatory myopathy (polymyositis)
Mitochondrial myopathy
Nemaline myopathy

HIV, human immunodeficiency virus.

### Progressive Multifocal Leukoencephalopathy (PML)

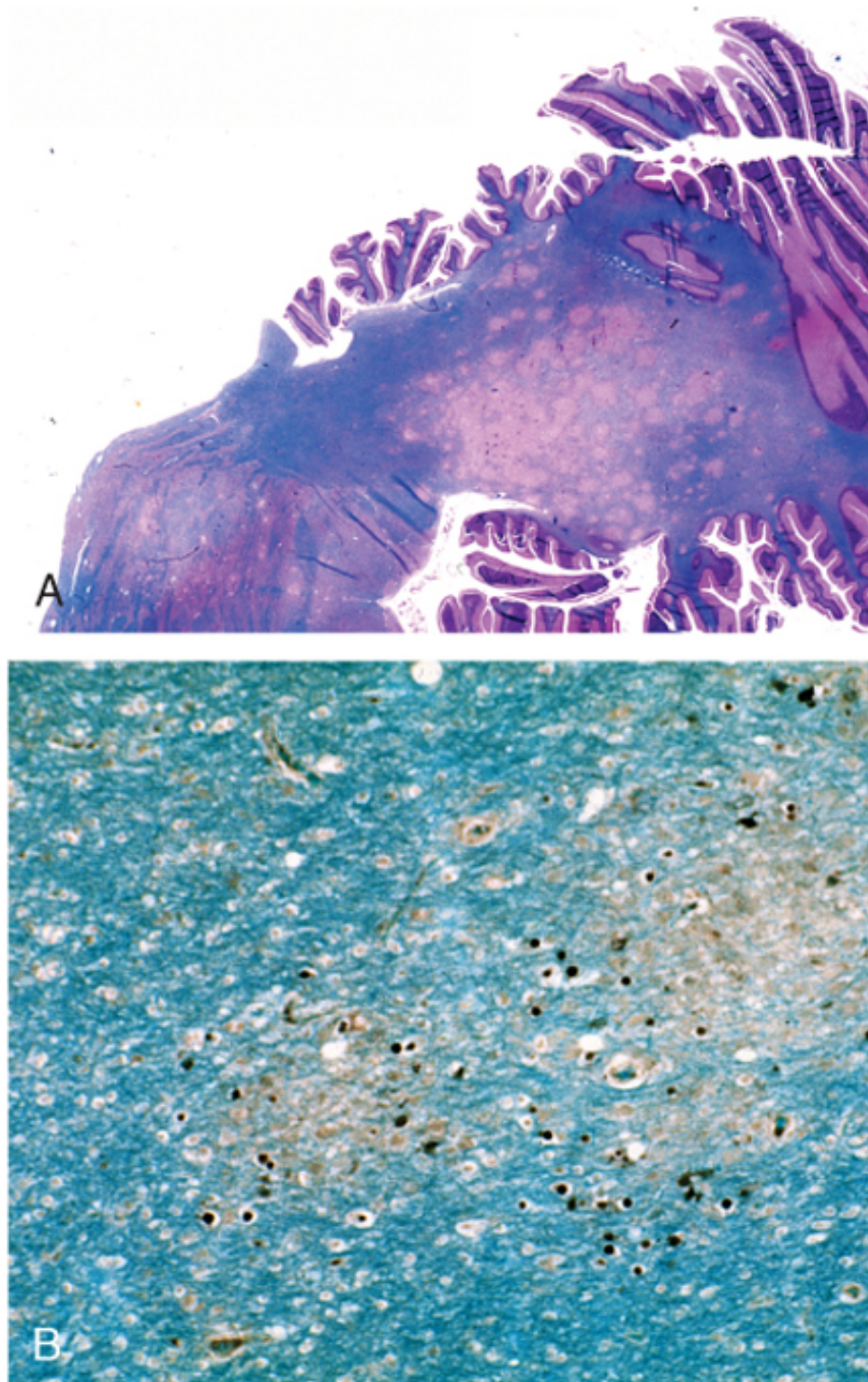
PML is caused by JC virus, a polyomavirus. The virus preferentially infects oligodendrocytes, so causing demyelination. The disease occurs almost invariably in immunosuppressed individuals in various clinical settings, including lymphoproliferative or myeloproliferative illnesses, immunosuppressive therapy, and AIDS. Most patients have been exposed to JC virus during childhood, and it is believed that PML results from virus reactivation. Patients develop focal and relentlessly progressive neurologic symptoms and signs, and imaging studies show enhancing lesions in the hemispheric or cerebellar white matter.

#### Morphology

The lesions consist of patches of irregular, ill-defined destruction of the white matter. As the disease progresses (Fig. 23-18). Each lesion is an area of demyelination, in the center containing lipid-laden macrophages and a reduced number of axons. At the edge of the lesion, oligodendrocyte nuclei whose chromatin is replaced by glassy, eosinophilic viral inclusions.



oligodendrocyte nuclei whose chromatin is replaced by glassy amphophilic viral inclusions. The virus also infects astrocytes, leading to bizarre giant forms with irregular, hyperchromatic, nuclei that can be mistaken for tumor.



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Figure 23-18 Progressive multifocal leukoencephalopathy. **A**, Section stained for myelin showing irregular, poorly confluent in places. **B**, Enlarged oligodendrocyte nuclei stained for viral antigens surrounded by a dense collection of smaller, dark-staining nuclei.

### **Fungal Encephalitis**

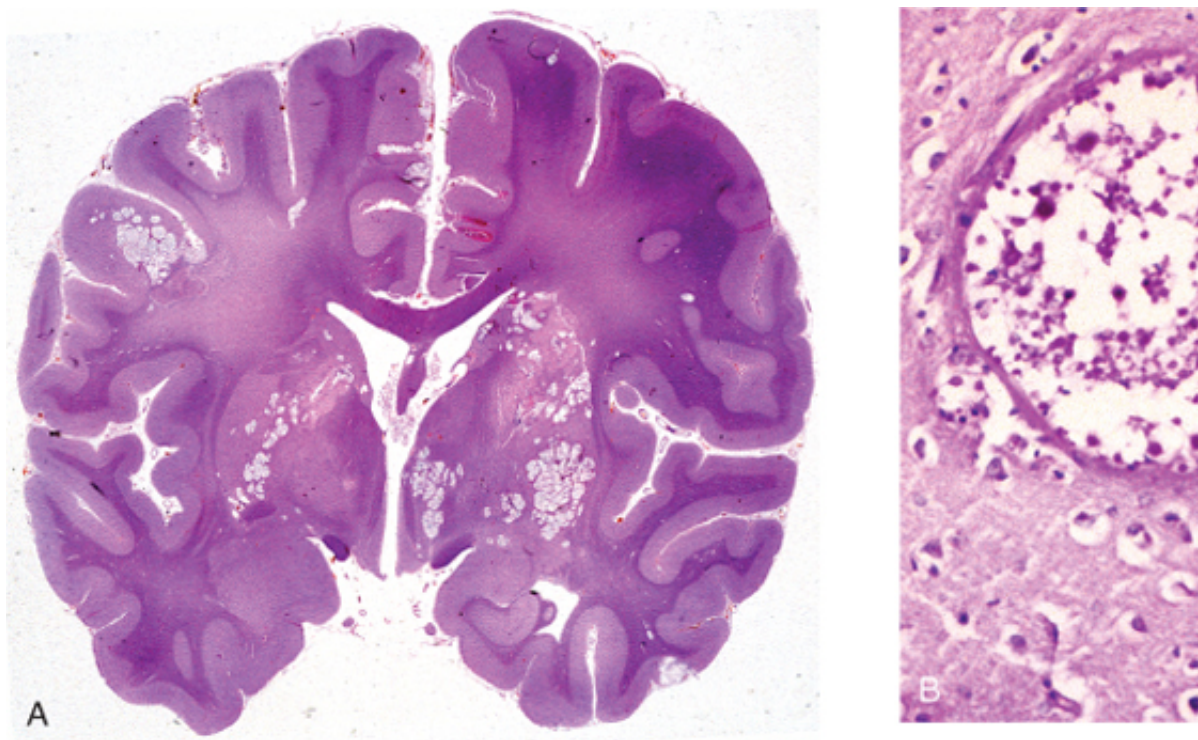
*Candida albicans*, *Mucor*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are the most common but in endemic areas, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis* in the setting of immunosuppression.

*Parenchymal invasion*, usually in the form of granulomas or abscesses, can occur with most of the meningitis. *Candida* usually produces multiple microabscesses, with or without granuloma formation by hematogenous dissemination, direct extension may also occur, particularly with *Mucor*, most *C. Aspergillus* tends to cause a distinctive pattern of widespread septic hemorrhagic infarctions because of blood vessel wall invasion and subsequent thrombosis.

*Cryptococcal meningitis and meningoencephalitis* is observed often in association with AIDS. It can be acute, weeks, or indolent, or it can evolve over months or years. The CSF may have few cells but a high concentration of encapsulated yeasts can be visualized in the CSF by India ink preparations and in tissue sections by silver stains (Fig. 23-19).

### **Other Meningoencephalitis**

While a wide range of other organisms can infect the nervous system and its covering, only three



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Figure 23-19 Cryptococcal infection. **A**, Whole-brain section showing the numerous areas of tissue destruction and perivascular spaces. **B**, At higher magnification it is possible to see the cryptococci.

### **Cerebral Toxoplasmosis**

Cerebral toxoplasmosis-infection with the protozoan *Toxoplasma gondii*-is one of the most common causes of morbidity in persons with AIDS. The clinical symptoms are subacute, evolving during a 1- or 2-week period. Computed tomography and magnetic resonance imaging studies can show multiple ring-enhancing lesions. The radiographic appearance is not pathognomonic.

### **Morphology**

The brain shows abscesses, frequently multiple, most often involving the cerebral (junction) and deep gray nuclei. Acute lesions consist of central foci of necrosis with surrounded by acute and chronic inflammation, macrophage infiltration, and vascular tachyzoites and encysted bradyzoites may be found at the periphery of the necrotic

### Cysticercosis

Cysticercosis is the consequence of an end-stage infection by the tapeworm *Tenia solium*. Because (inappropriate) host, larvae that inadvertently infect humans will encyst. These cysts can be found common within the brain and subarachnoid space. They typically present as a mass lesion and can intensify when the organism dies within the cyst, as happens after therapy.

#### Morphology

The organism is encysted within a smooth lining; around the cyst, there is often a reaction. The body wall and hooklets from mouth parts are most commonly recognized. If the organism has died, there can be an intense inflammatory infiltrate that will often contain eosinophils.

*Amebic meningoencephalitis* has different patterns of disease with different species of the parasite swimming in nonflowing warm fresh water, causes a rapidly fatal necrotizing encephalitis. In contrast to granulomatous meningoencephalitis.

### Prion Diseases

This group of diseases includes sporadic, familial, iatrogenic and variant forms of Creutzfeldt-Jakob diseases from this group are also known, including scrapie in sheep and goats and bovine spongiform disease). All these disorders are associated with abnormal forms of a normal cellular protein, termed PrP<sup>C</sup>. This form of this protein can act as an infectious agent, since it propagates itself and injures the cells in which it is found. Prion diseases are either sporadic or associated with mutations in the gene that encodes PrP<sup>C</sup>.

The unique pathogenesis of prion diseases is related to changes in the conformation of PrP from its native configuration called either PrP<sup>Sc</sup> (for scrapie) or PrP<sup>res</sup> (for protease resistant) (Fig. 23-20). In the process, PrP becomes resistant to protease digestion. Once formed, PrP<sup>Sc</sup> can then initiate comparable transmissible disease. The infectious nature of PrP<sup>Sc</sup> protein comes from this ability to propagate the pathologic conformation. Prion disease can occur spontaneously at an extremely low rate and accounts for sporadic cases of prion disease. If an individual encoding PrP<sup>C</sup>, then the change can occur at a higher rate; this results in familial forms of prion disease.

Accumulation of PrP<sup>Sc</sup> in neural tissue seems to be the cause of cell injury, but how this material leads to vacuoles and eventual neuronal death is still unknown.

#### Creutzfeldt-Jakob Disease

CJD is a rare but well-characterized prion disease that manifests clinically as a rapidly progressive dementia. Cases, with a worldwide annual incidence of about 1 per million; familial forms also exist. The disease lasts a few years. There are well-established cases of iatrogenic transmission by deep implantation electrodes and by human growth hormone. The clinical presentation begins with subtle changes in memory and behavior. The disease is uniformly fatal, with an average duration of only 7 months.

#### Morphology

The progression of the dementia in CJD is usually so rapid that there is little, if any, brain atrophy. On microscopic examination, the pathognomonic finding is a **spongiform degeneration of the cerebral cortex and deep gray matter structures** (caudate, putamen); this is a process that results in the uneven formation of small, apparently empty, microscopic spaces within the neuropil and sometimes in the perikaryon of neurons (Fig. 23-20A). There is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated spaces ("status spongiosus"). No inflammatory infiltrate is present. In all forms of prion disease, immunohistochemical staining demonstrates the presence of proteinase K-resistant PrP<sup>Sc</sup>.





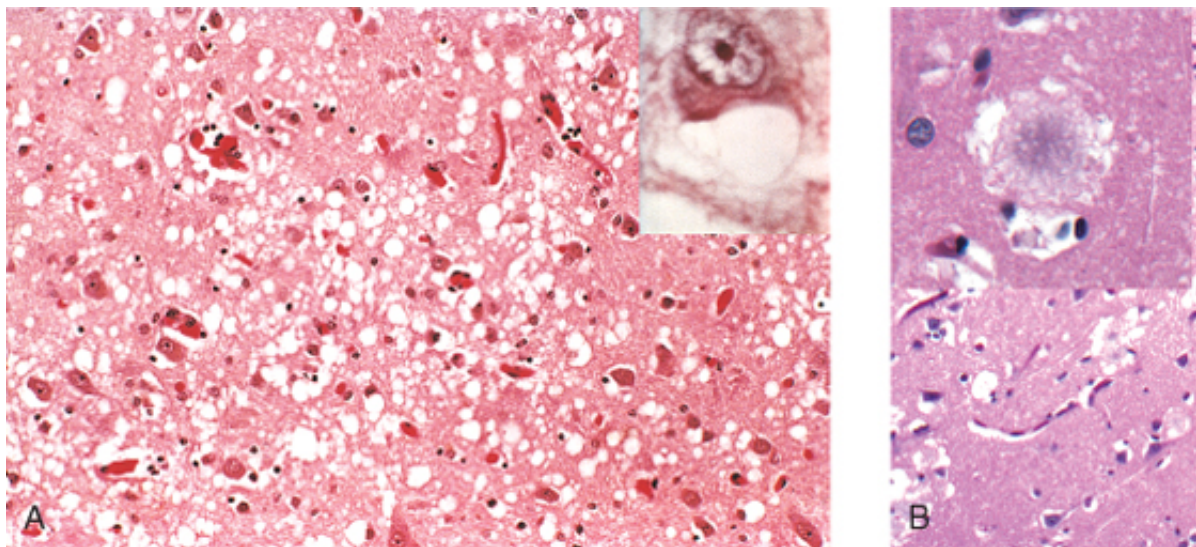


## Variant Creutzfeldt-Jakob Disease

Starting in 1995, a series of cases with a CJD-like illness appeared in the United Kingdom. They had two important respects: the disease affected young adults, behavioral disorders figured prominently in the neurologic syndrome progressed more slowly than in individuals with other forms of CJD. The new features of these new cases were similar to those of CJD, suggesting a close relationship between the two. Evidence indicates that this new disease is a consequence of exposure to the prion disease of cattle. vCJD has a similar pathologic appearance, in general, to other forms of CJD, with spongiform change in the cerebral cortex. vCJD, however, there are abundant cortical amyloid plaques, surrounded by spongiform change (

### SUMMARY

**Infections of the Nervous System** Pathogens from viruses through parasites, in addition, prion disease represents a form of protein-induced transmissible disease of the nervous system. Different pathogens may use distinct routes to reach the brain, resulting in different patterns of disease. Bacterial infections may cause meningitis, cerebritis, or chronic meningoencephalitis. Viral infections can cause meningitis or meningoencephalitis, affect the brain directly with a meningoencephalitis or by increasing the risk of other infections (toxoplasmosis, CMV) or CNS lymphoma. Prion diseases are transmitted by the conversion of a normal cellular protein. They can be sporadic, transmitted, or inherited.



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Figure 23-21 Prion disease. **A**, Histology of CJD showing spongiform change in the cerebral cortex. *Inset*, High magnification view of CJD (vCJD) is characterized by amyloid plaques (see *inset*) that sit in the regions of greatest spongiform change.





## TUMORS

The annual incidence of tumors of the CNS ranges from 10 to 17 per 100,000 persons for intracranial tumors; about half to three-quarters are primary tumors, and the rest are metastatic. CNS tumors are the proportion of cancers of childhood, accounting for as many as 20% of all tumors. CNS tumors are classified by histologic subtype and location. In childhood, tumors are likely to arise in the posterior fossa, while in adults, they are more likely to arise in the supratentorial region.

Tumors of the nervous system have unique characteristics that set them apart from neoplastic processes in other organs.

Histologic distinction between benign and malignant lesions may be more subtle in the CNS than in other organs. The slow growth of low-grade lesions (low mitotic rate, cellular uniformity, and slow growth) may still be clinically significant, thereby leading to serious clinical deficits and poor prognosis. The anatomic site of the tumor determines the consequences irrespective of histologic classification; for example, a benign meningioma, if large enough, can cause cardiorespiratory arrest. Moreover, the ability to resect a lesion may be limited because of its location. The biology of primary CNS neoplasms differs from that of other tumors. Although even the most highly malignant tumors can be resected outside the CNS, the subarachnoid space does provide a pathway for spread so that seeding of other sites can occur.

### Gliomas

Gliomas are tumors of the brain parenchyma that histologically resemble different types of glial cells. The major categories are *astrocytomas*, *oligodendrogliomas*, and *ependymomas*.

#### **Astrocytoma**

Several different categories of astrocytic tumors are recognized, the most common being fibrillary astrocytomas. Astrocytomas have characteristic histologic features, distribution within the brain, age groups typical of occurrence, and clinical course.

##### Fibrillary Astrocytoma

Fibrillary astrocytomas account for about 80% of adult primary brain tumors. They are most frequently found in the cerebral hemispheres. The most common presenting signs and symptoms are focal neurologic deficits related to the anatomic site of involvement. Fibrillary astrocytomas show a wide range of histologic features that correlates well with clinical course and outcome. Based on the degree of differentiation, they are classified as fibrillary astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme, the least differentiated of all.

For well-differentiated astrocytomas, symptoms can be static or progress only slowly during a number of years. Eventually, however, patients usually enter a period of more rapid clinical deterioration. This is usually associated with the appearance of anaplastic features and more rapid growth of the tumor. Many patients present with symptoms that suggest a more aggressive tumor than having their tumor evolve from a lower grade lesion. Independent of the initial lesion, the prognosis is usually very poor. Current state-of-the-art treatment, comprising resection (when feasible) together with radiotherapy, results in a mean survival of only 8 to 10 months; fewer than 10% of patients are alive after 2 years.

#### **Morphology**

The macroscopic appearance of fibrillary astrocytoma is that of a poorly defined, gelatinous mass that expands and distorts the invaded brain (Fig. 23-22A). Infiltration beyond the gross margins is always present. The cut surface of the tumor is either firm, or soft and gelatinous; cystic areas may be seen. In glioblastoma, variation in the gross appearance of the tumor from region to region is common (Fig. 23-22B). Some areas are firm and white, others are soft and yellow (the result of necrosis), and yet others show regions of cystic degeneration and hemorrhage.

Well-differentiated fibrillary astrocytomas are characterized by a mild to moderate increase in glial cell nuclei, somewhat variable nuclear pleomorphism, and an intervening fibrillary background of astrocytic cell processes that give the background a fibrillary appearance. The transition between tumor and normal tissue is indistinct, and tumor cells can be seen infiltrating normal tissue.



the main lesion. Anaplastic astrocytomas show regions that are more densely cellular with nuclear pleomorphism; increased mitoses are often observed. The highest grade tumor, glioblastoma, has a histologic appearance similar to anaplastic astrocytoma with the **necrosis and vascular or endothelial cell proliferation and pseudo-palisading**. High-grade astrocytomas have abnormal vessels that are "leaky" and will show contrast enhancement on imaging studies.

#### Pilocytic Astrocytoma

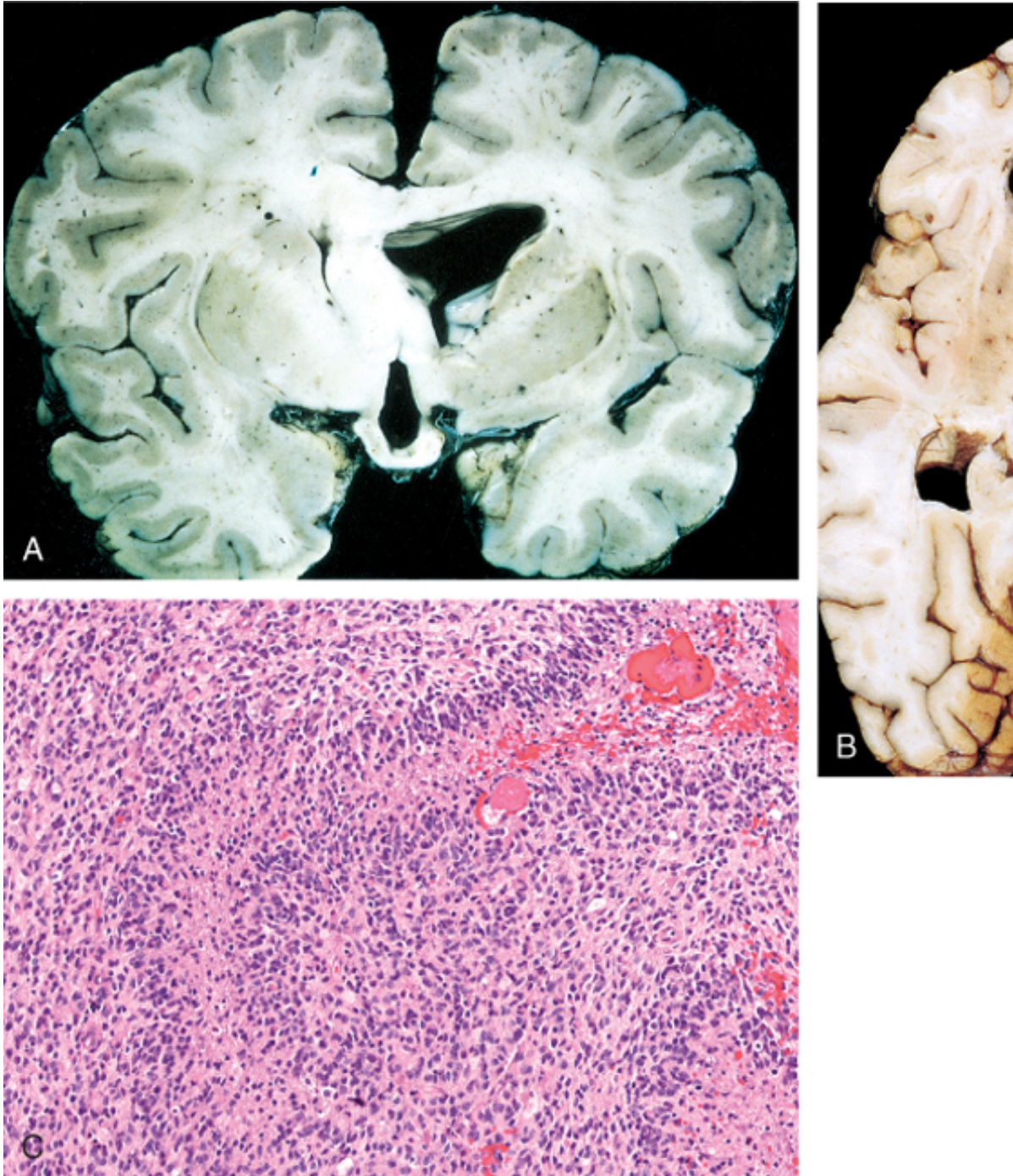


Figure 23-22 Astrocytomas. **A**, Low-grade astrocytoma is seen as expanded white matter of the left cerebral hemisphere. **B**, Glioblastoma appearing as a necrotic, hemorrhagic, infiltrating mass. **C**, Glioblastoma is a densely cellular tumor with many tumor cell nuclei.

Pilocytic astrocytomas are relatively benign tumors, often cystic, that typically occur in children and the cerebellum but may also appear in the floor and walls of the third ventricle, the optic nerves, and the cerebral hemispheres. Symptomatic recurrence from incompletely resected lesions is often associated with the solid component. Tumors that extend into the hypothalamic region from the optic tract can have a poor prognosis.

### **Morphology**

A pilocytic astrocytoma is often cystic, with a mural nodule in the wall of the cyst; if solid, it is well circumscribed. The tumor is composed of areas with bipolar cells with long, thin "hair-like" processes. GFAP positive; Rosenthal fibers, eosinophilic granular bodies, and microcysts are often present, and mitoses are absent.

### **Oligodendroglioma**

These tumors constitute about 5% to 15% of gliomas and are most common in the fourth and fifth decades of life. They are often associated with neurologic complaints, often including seizures. The lesions are found mostly in the cerebral white matter.

Patients with oligodendrogliomas have a better prognosis than do patients with astrocytomas. Combined surgery, chemotherapy, and radiotherapy yields an average survival of 5 to 10 years. Patients with anaplastic oligodendrogliomas have a poorer prognosis. The most common genetic findings are loss of heterozygosity for chromosomes 1p and 19q. These changes have a consistent and long-lasting response to chemotherapy and radiation.

### **Morphology**

Oligodendrogliomas are infiltrative tumors that form gelatinous, gray masses, and may be associated with hemorrhage, and calcification. On microscopic examination, the tumor is composed of cells with spherical nuclei containing finely granular chromatin (similar to normal oligodendrocytes) and a clear halo of cytoplasm (Fig. 23-23A). The tumor typically contains a delicate network of capillaries. Calcification, present in as many as 90% of these tumors, ranges from small, punctate to massive deposits. Mitotic activity is usually very difficult to detect. With increasing anaplasia, increased mitotic activity and necrosis, the tumor becomes a high-grade glioma (anaplastic oligodendroglioma).

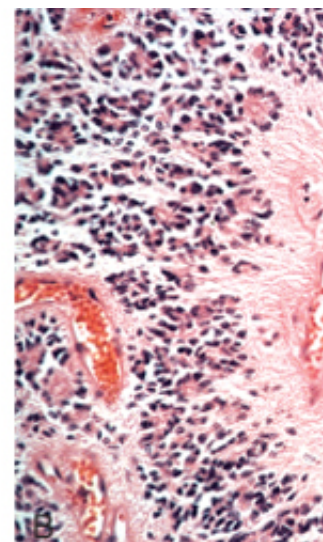
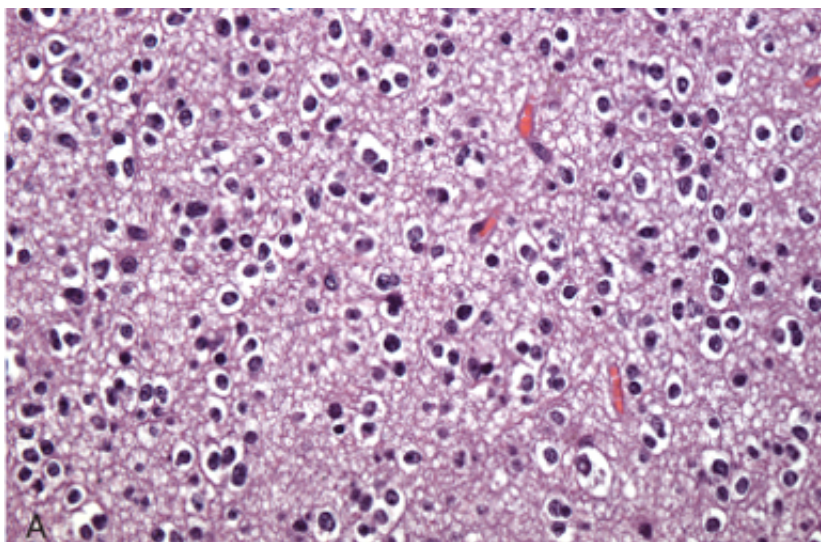




Figure 23-23 Other gliomas. **A**, In oligodendroglioma tumor cells have round nuclei, often with a cytoplasmic halo. They form an interlacing pattern. **B**, Microscopic appearance of ependymoma.

### **Ependymoma**

Ependymomas most often arise next to the ependyma-lined ventricular system, including the cerebellum. In the first decades of life, they typically occur near the fourth ventricle and constitute 5% to 10% of the primary brain tumors. In adults, the spinal cord is their most common location; tumors in this site are particularly frequent in the posterior horn (see below). Because ependymomas usually grow within the ventricles, CSF dissemination is a common feature. Prognosis for completely resected supratentorial and spinal ependymomas is better than for those in the posterior horn.

#### **Morphology**

In the fourth ventricle, ependymomas are typically solid or papillary masses extending into the ventricle. These tumors are composed of cells with regular, round to oval nuclei with dense chromatin. Between the nuclei there is a variably dense fibrillary background. Tumors may form elongated structures (**rosettes**, canals) that resemble the embryologic ependymal processes extending into a lumen (Fig. 23-23B); more frequently present are **perivascular pseudorosettes** in which tumor cells are arranged around vessels with an intervening zone consisting of fine fibrillary processes directed toward the wall of the vessel. Anaplastic ependymomas show increased mitotic rates, necrosis, and less evident ependymal differentiation.

### **Neuronal Tumors**

*Central neurocytoma* is a low-grade neuronal neoplasm found within and adjacent to the ventricular system (usually the third ventricle), characterized by evenly spaced, round, uniform nuclei and often islands of neurofibrillary material.

*Gangliogliomas* are tumors with a mixture of glial elements (looking like a low-grade astrocytoma) and neuronal elements. These tumors are slow growing, but the glial component occasionally becomes frankly anaplastic. These lesions often present with seizures.

*Dysembryoplastic neuroepithelial tumor* is a distinctive, low-grade tumor of childhood, showing slow growth and a good prognosis after resection; it often presents as a seizure disorder. These lesions are typically located in the subcortical white matter and consist of small round cells with features of neurons arranged in columns and around central cores of poorly cellular, discrete intracortical nodules that have a myxoid background. There are well-differentiated "floating" mucopolysaccharide-rich fluid of the myxoid background.

### **Poorly Differentiated Neoplasms**

Some tumors, though of neuroectodermal origin, express few if any of the phenotypic markers of the mature nervous system. The most common is the *medulloblastoma*, accounting for 20% of pediatric brain tumors.

### **Medulloblastoma**

This tumor occurs predominantly in children and exclusively in the cerebellum. Neuronal and glial components are often largely undifferentiated. The tumor is highly malignant, and the prognosis for untreated disease is poor. With total excision and radiation, the 5-year survival rate may be as high as 50%. A poor degree of differentiation can be found elsewhere in the nervous system (called CNS primitive neuroectodermal tumor).

#### **Morphology**

In children, medulloblastomas are located in the midline of the cerebellum; lateral in adults. The tumor is often well circumscribed, gray, and friable, and may be seen between the cerebellar folia and involving the leptomeninges (Fig. 23-24A). Medulloblastoma consists of sheets of anaplastic ("small blue") cells (Fig. 23-24B). Individual tumor cells are small with scant cytoplasm and hyperchromatic nuclei; mitoses are abundant.

## Other Parenchymal Tumors

### **Primary Central Nervous System Lymphoma**

Primary CNS lymphoma accounts for 2% of extranodal lymphomas and 1% of intracranial tumors in immunosuppressed individuals (including transplant recipients and persons with AIDS); under these conditions, they are nearly all driven by Epstein-Barr virus. In nonimmunosuppressed populations the age spectrum is increasing after 60 years of age; most of these tumors are diffuse large B-cell lymphomas. Regardless, primary CNS lymphoma is an aggressive disease with relatively poor response to chemotherapy as compared with systemic lymphoma.

Individuals with primary brain lymphoma often have multiple sites of tumor within the brain parenchyma. Systemic involvement outside of the CNS is a rare and late complication. Conversely, lymphoma arising outside the CNS is rarely found in the parenchyma; when it does occur, there is usually tumor within the CSF and around intradural nerve roots.

#### **Morphology**

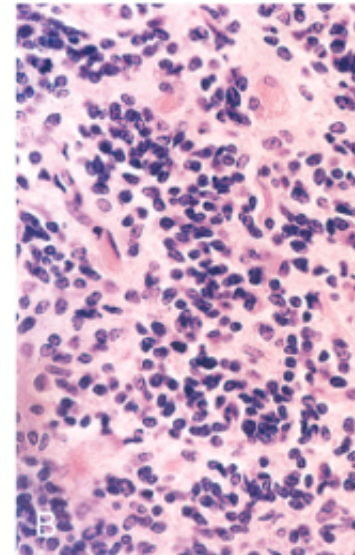
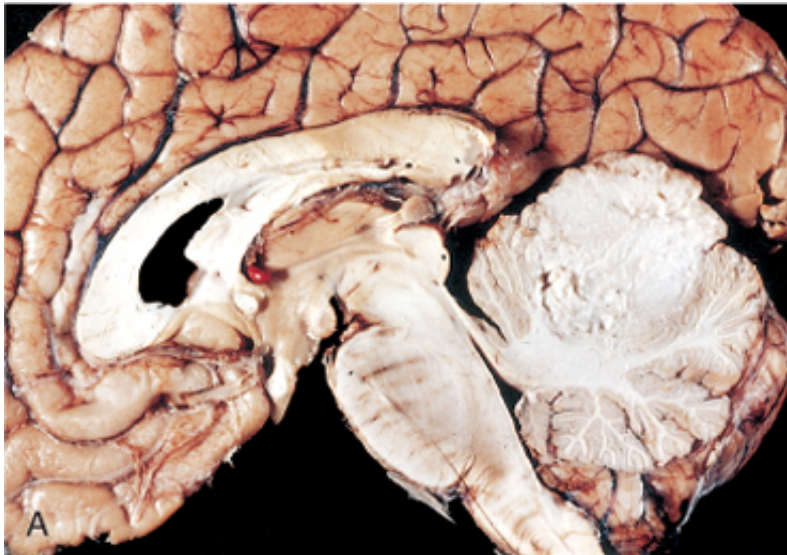
Lesions often involve deep gray structures, as well as white matter and cortex. Perivascular cuffing is common. The tumors are relatively well defined as compared with glial neoplasms and metastases. They often show extensive areas of central necrosis. The tumors are most commonly large-cell lymphomas, although other histologic types can be observed. In all lesions, malignant cells infiltrate the parenchyma of the brain and accumulate around blood vessels.

### **Germ-Cell Tumors**

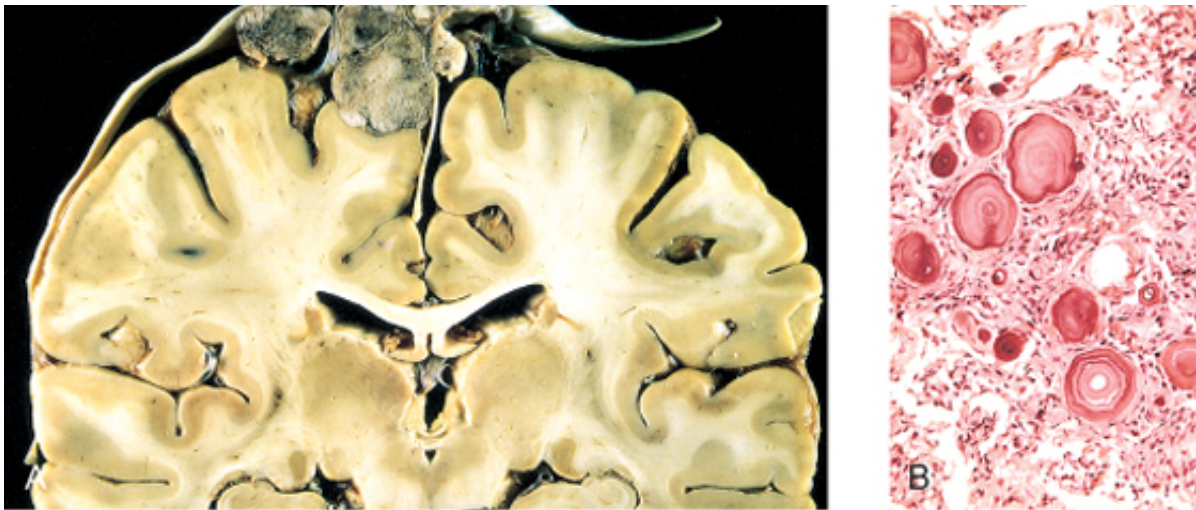
Primary brain germ-cell tumors occur along the midline, most commonly in the pineal and the suprasellar regions. They account for 1% of brain tumors in people of European descent but as many as 10% of brain tumors in Japan, 90% occurring during the first two decades. Germ-cell tumors in the pineal region show a strong relationship to the pineal gland.

Germ-cell tumors in the brain share many of the features of their counterparts in the gonads. The histologic pattern of the CNS tumor is similar to that used in the testis ([Chapter 18](#)), although the CNS tumor that is the counterpart of the testicular seminoma is the germinoma. CNS involvement by a gonadal germ-cell tumor is not uncommon.

### **Meningiomas**



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Figure 23-24 Medulloblastoma. **A**, Sagittal section of brain showing medulloblastoma destroying the superior medulla and cerebellum. **B**, Microscopic view of medulloblastoma.



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Figure 23-25 Meningioma. **A**, Parasagittal multilobular meningioma attached to the dura with compression of underlying brain tissue. **B**, Histologic section showing syncytial cells, fibroblastic areas, and numerous psammoma bodies.

Meningiomas are predominantly benign tumors of adults, usually attached to the dura, and arising from the arachnoid. Meningiomas may be found along any of the external surfaces of the brain as well as within the brain parenchyma. They usually arise from the stromal arachnoid cells of the choroid plexus. They usually come to attention because of focal findings referable to compression of underlying brain. When a person has multiple meningiomas, a possible diagnosis of neurofibromatosis type 2 (NF2) is considered. About half of meningiomas not associated with NF2 still have mutations in the *NF2* gene on the long arm of chromosome 22.

### Morphology

Meningiomas grow as well-defined dural-based masses that compress underlying brain tissue and are separated from it (Fig. 23-25A). Extension into the overlying bone may be present. The histologic patterns found in meningiomas, including: **syncytial**, named for the whorled appearance of cells in tight groups without visible cell membranes; **fibroblastic**, with elongated cells and collagen deposition between them; **transitional**, which shares features of the syncytial and fibroblastic patterns; **psammomatous**, with numerous psammoma bodies (Fig. 23-25B); **secretory**, with intracytoplasmic droplets and intracellular lumina by electron microscopy; and **microcystic**, with a spongy appearance.

**Atypical meningiomas**-lesions with a higher rate of recurrence, more aggressive behavior, and a possible need for therapy in addition to surgery-are recognized by several histologic features, including a higher mitotic rate.

**Anaplastic (malignant) meningiomas** are highly aggressive tumors that resemble glioblastoma, although there is usually some histologic evidence that indicates a meningothelial origin.

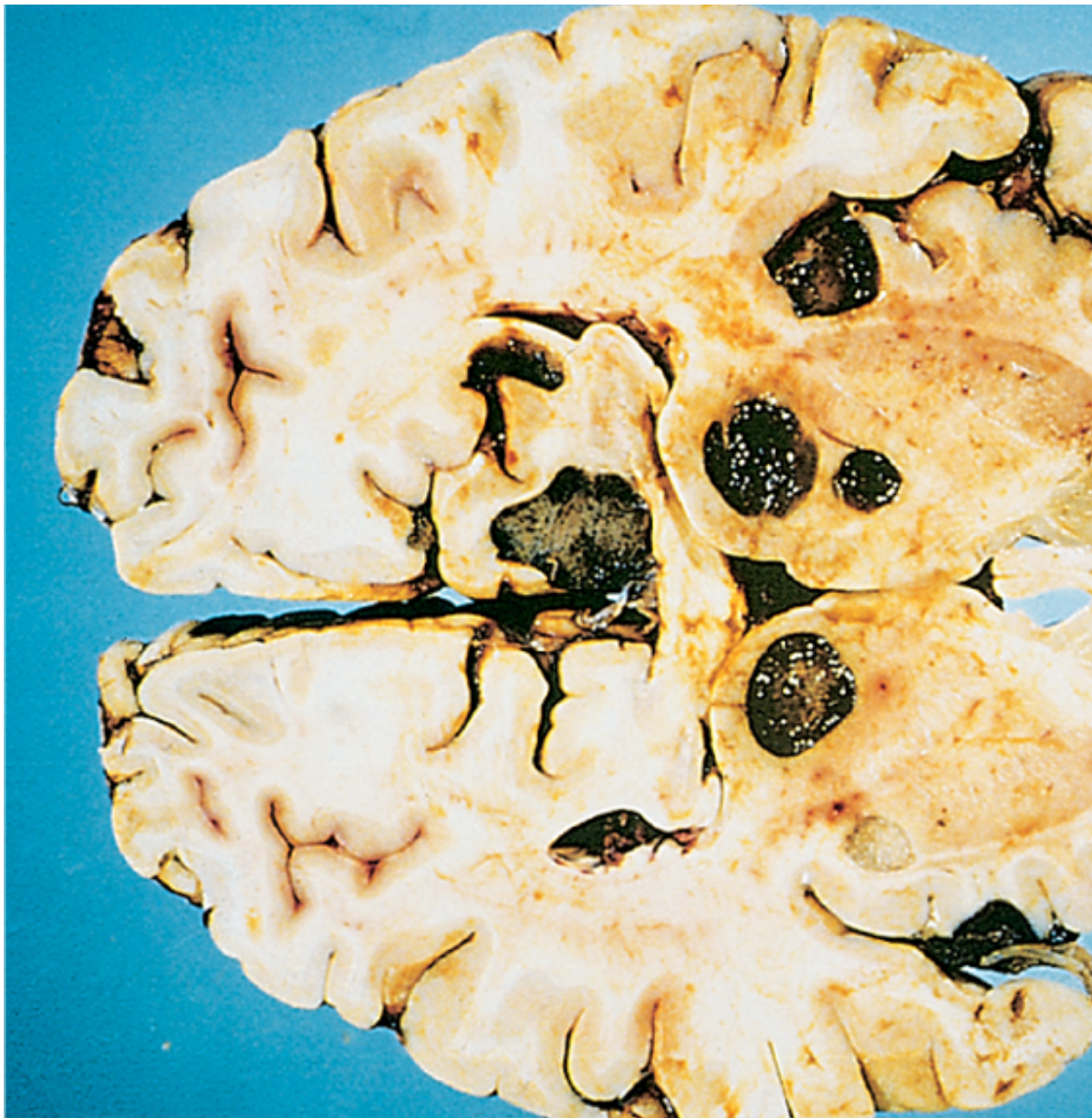
Although most meningiomas are easily separable from underlying brain, some tumors show evidence of brain invasion, which is associated with increased risk of recurrence.

The overall prognosis of meningiomas is influenced by the size and location of the lesion, surgical resectability, and the presence of atypical features.

### Metastatic Tumors

Metastatic lesions, mostly carcinomas, account for approximately a quarter to half of intracranial tumors. The most common primary sites are lung, breast, skin (melanoma), kidney, and gastrointestinal tract, accounting for approximately 80% of metastatic tumors. The meninges are also a frequent site of involvement by metastatic disease. In the brain, metastatic lesions are often at the gray matter-white matter junction, usually surrounded by a zone of edema (Fig. 23-26). The tumor parenchyma is well defined microscopically as well, with surrounding reactive gliosis.





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Figure 23-26 Metastatic melanoma. Metastatic lesions are distinguished grossly from most primary CNS tumor margins. The dark pigment in the tumor nodules in this case is characteristic of most m

In addition to the direct and localized effects produced by metastases, *paraneoplastic syndromes* affect various organs and nervous systems, sometimes even preceding the clinical recognition of the malignant neoplasm. They are often associated with small-cell carcinoma of the lung. Many, but not all, individuals with paraneoplastic syndromes have detectable tumor antigens. There are several manifestations of paraneoplastic syndromes; some characteris

*Subacute cerebellar degeneration* resulting in ataxia, with destruction of Purkinje cells, gliosis, and loss of sensory neurons from dorsal root ganglia, in association with inflammation. *Limbic encephalitis* causing a subacute dementia, with perivascular inflammatory cell infiltrate, loss, and gliosis, all centered in the medial temporal lobe. *Subacute sensory neuropathy* leading to sensory neuron loss, in association with inflammation.

## SUMMARY



**Tumors** Tumors of the nervous system may arise from the cells of the cover cells intrinsic to the brain (gliomas, neuronal tumors, choroid plexus tumors) within the skull (primary CNS lymphoma, germ-cell tumors), or they may spread to the body (metastases). Even low-grade or benign tumors can have a poor clinical course depending on where in the brain they occur. Glial tumors are broadly classified into astrocytomas, oligodendrogliomas, and ependymomas. Increasing tumor malignancy is associated with cytologic anaplasia, increased cell density, necrosis, and mitotic activity. The most poorly differentiated glial tumor is glioblastoma; it contains anaplastic astrocytic features and vascular abnormalities. Metastatic spread of brain tumors to other regions of the brain is not comparably protected against spread of tumors from elsewhere. Extracranial tumors are commonly metastatic to the nervous system than lymphoid malignancies; sarcomas metastasize to the brain.



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## PRIMARY DISEASES OF MYELIN

Within the CNS, axons are tightly ensheathed by myelin, which serves as an electrical insulator to allow rapid propagation of impulses. Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes, with most of the cytoplasm excluded. These portions of the oligodendrocyte membrane contain specialized proteins and lipids that contribute to the orderly packing of the layers. An oligodendrocyte extends processes toward many different axons and wraps a segment of roughly a few hundred microns of axon. Each of these segments is called an *internode*, and the gaps between internodes are known as *nodes of Ranvier*. Although myelinated axons are present in all areas of the brain, they are the dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders.

The myelin in peripheral nerves is similar to the myelin in the CNS but has several important differences: Peripheral myelin is made by Schwann cells, not oligodendrocytes; each cell in the peripheral nerve contributes to only one internode, while in the CNS, many internodes come from a single oligodendrocyte; and the specialized proteins and lipids are also different. Therefore, most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.

If the myelin along a set of axons is disrupted, there are changes in the ability of these axons to transmit signals. The symptoms of diseases of myelin are related to this disruption of neuronal communication; the exact nature of the symptoms depends on the site (or sites, since most diseases of myelin affect many regions of the brain at the same time) where myelin disruption occurs. The natural history of demyelinating diseases is determined, in part, by the limited capacity of the CNS to regenerate normal myelin and by the degree of secondary damage to axons that occurs as the disease runs its course.

In general, diseases involving myelin are separated into two broad groups. *Demyelinating diseases* of the CNS are acquired conditions characterized by preferential damage to previously normal myelin. The most common diseases in this group result from immune-mediated injury, such as multiple sclerosis (MS) and related disorders. Other processes that can cause this type of disease include viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy (see above), and injury caused by drugs and other toxic agents.

In contrast, when myelin is not formed properly or has abnormal turnover kinetics, the resulting diseases are referred to as *dysmyelinating*. As would be expected, dysmyelinating diseases are associated with mutations affecting the proteins required for formation of normal myelin or in mutations that affect the synthesis or degradation of myelin lipids. The other general term for these diseases is *leukodystrophy*.

### Multiple Sclerosis

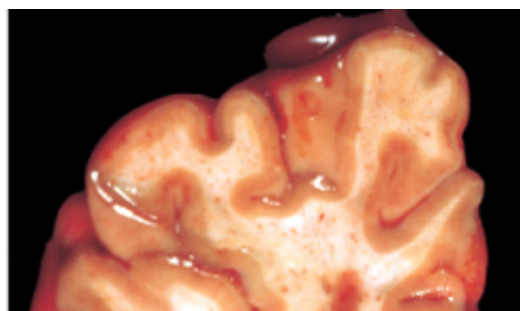
MS is an autoimmune demyelinating disorder characterized by *distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space*. It is the most common of the demyelinating disorders, having a prevalence of approximately 1 per 1000 persons in most of the United States and Europe. The disease becomes clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare. Women are affected twice as often as men. In most individuals with MS the illness shows relapsing and remitting episodes of neurologic deficits. The frequency of relapses tends to decrease during the course of the illness, but there is a steady neurologic deterioration in a subset of patients.

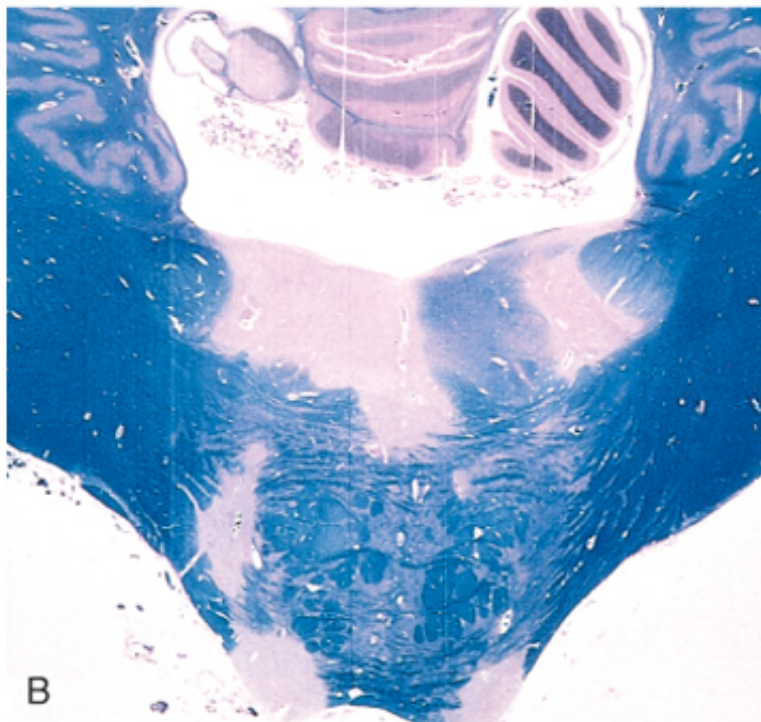
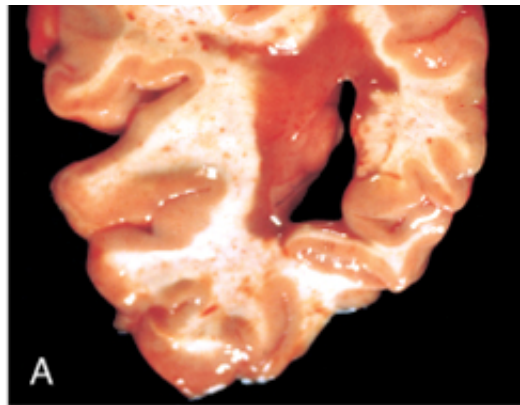
It is believed that MS, like other autoimmune diseases, is caused by a combination of environmental and genetic factors that result in a loss of tolerance to self proteins (in this case, myelin antigens). A transmissible agent has been proposed, but none has ever been conclusively identified. The risk of developing MS is 15-fold higher when the disease is present in a first-degree relative. The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for dizygotic twins; this indicates a strong, but not causative, role for genes. Genetic linkage of MS susceptibility to the HLA-DR2 extended haplotype is also well established.

Given the prominence of chronic inflammatory cells within and around MS plaques, immune mechanisms that may cause myelin destruction have been the focus of much investigation. Experimental allergic encephalomyelitis is an animal model of MS in which demyelination and inflammation occur after immunization with myelin, myelin proteins, or certain peptides from myelin proteins. In this model, the lesions are caused by a T cell-mediated delayed type hypersensitivity reaction to myelin proteins, and the same immune mechanism is thought to be central to the pathogenesis of MS. While MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur. Toxic effects of lymphocytes, macrophages, and their secreted molecules have been implicated in initiating the process of axonal injury, sometimes even leading to neuronal death.

### Morphology

MS is a white matter disease; abnormalities on the surface of the brain are usually restricted to those regions where myelinated fiber tracts course superficially (brain stem and spinal cord). Affected areas show multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions, termed **plaques** (Fig. 23-27A). These commonly occur beside the ventricles. They are also frequent in the optic nerves and chiasm, brain stem, ascending and descending fiber tracts, cerebellum, and spinal cord. The lesions have sharply defined borders at the microscopic level (Fig. 23-27B). In an **active plaque** there is evidence of ongoing myelin breakdown with abundant macrophages containing myelin debris. Lymphocytes and monocytes are present, mostly as perivascular cuffs. Small active lesions are often centered on small veins. Axons are relatively preserved, although they may be reduced in number. When plaques become quiescent (**inactive plaques**), the inflammation mostly disappears, leaving behind little to no myelin. Instead, astrocytic proliferation and gliosis are prominent. There can also be **shadow plaques**, where the border between normal and affected white matter is not sharply circumscribed. Here, thinned-out myelin sheaths can be demonstrated, especially at the outer edges, suggesting that this border region represents either incomplete myelin loss or partial remyelination.





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 Figure 23-27 Multiple sclerosis. **A**, Section of fresh brain showing a plaque around occipital horn of the lateral ventricle. **B**, Unstained regions of demyelination (MS plaques) around the fourth ventricle. (Luxol fast blue-PAS stain for myelin.)

### Clinical Features

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The course of MS is variable, but commonly there are multiple episodes of new symptoms (*relapses*) followed by episodes of recovery (*remissions*); typically, the recovery is not complete. The consequence of this pattern of relapsing-remitting disease is the gradual, often stepwise, accumulation of increasing neurologic deficits. Although MS lesions can occur anywhere in the CNS and, as a consequence, may induce a wide range of clinical manifestations, certain patterns of neurologic symptoms and signs are commonly observed. Unilateral visual impairment occurring over the course of a few days is a frequent initial manifestation of MS; it is due to involvement of the optic nerve (*optic neuritis*, *retrobulbar neuritis*). When this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown MS. Involvement of the brain stem produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements. Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder



impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function. Changes in cognitive function can be present, but are often much milder than the other findings. In any individual patient it is hard to predict when the next relapse will occur; most current treatments aim at decreasing the rate and severity of relapses rather than recovering lost function.

The CSF in MS patients shows a mildly elevated protein level with an increased proportion of  $\gamma$ -globulin; in one-third of cases there is moderate pleiocytosis. When the immunoglobulin is examined further, most MS patients show *oligoclonal bands*, representing antibodies directed against a variety of antigenic targets. Although these antibodies constitute a marker for disease activity, it is not clear if they are a critical part of the disease mechanism.

Magnetic resonance imaging has greatly added to the understanding of MS, since it can show the distribution of lesions across the nervous system during active disease. From this work it has become clear that there are often more lesions in the brains of MS patients than might be expected by clinical examination, and that lesions can come and go much more often than was previously suspected.

### Other Acquired Demyelinating Diseases

Immune-mediated demyelination can be found after a number of systemic infectious illnesses, including relatively mild viral diseases. These are not thought to be related to direct spread of the infectious agents to the nervous system. It is believed that the immune response to pathogen-associated antigens cross-reacts with myelin antigens, and that this results in myelin damage.

There are two general patterns of post-infectious pathology involving autoimmune reaction to myelin; unlike MS, they are monophasic illnesses with relatively abrupt onset. With *acute disseminated encephalomyelitis*, symptoms typically develop a week or two after the antecedent infection and suggest diffuse brain involvement with headache, lethargy, and coma rather than the focal findings typical of MS. Symptoms progress rapidly, with a fatal outcome in as many as 20% of cases; in the remaining patients there is complete recovery. *Acute necrotizing hemorrhagic encephalomyelitis* is a more devastating related disorder, which typically affects young adults and children.

*Central pontine myelinolysis* is a nonimmune process characterized by loss of myelin involving the center of the pons, most often after rapid correction of hyponatremia. It occurs in a variety of clinical settings including alcoholism and severe electrolyte or osmolar imbalance. Although the most characteristic lesion occurs in the pons, similar lesions can be found elsewhere in the brain. Because of the involvement of fibers in the pons carrying signals to motor neurons in the spinal cord, patients often present with rapidly evolving quadriplegia.

As discussed earlier, progressive multifocal leukoencephalopathy is a demyelinating disease that occurs following reactivation of JC virus in immunosuppressed patients.

### Leukodystrophies

*Leukodystrophies* are inherited dysmyelinating diseases in which the clinical symptoms derive from either abnormal myelin synthesis or turnover. Some of these disorders involve lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins. Most are autosomal recessive, although X-linked diseases occur ([Table 23-2](#)).

#### Morphology

Much of the pathology of leukodystrophies is found in the white matter, which is diffusely abnormal in color (gray and translucent) and volume (decreased). Some diseases may show patchy involvement early, while others have a predilection for occipital lobe involvement as they begin. In the end, though, nearly all of the white matter is usually affected. With

the end, though, nearly all of the white matter is usually affected. With the loss of white matter, the brain becomes atrophic, the ventricles enlarge, and secondary changes can be found in the gray matter. Myelin loss is common across the leukodystrophies, often with macrophages stuffed with lipid. Some of the diseases also show specific inclusions, related to the accumulation of particular lipids.

### Clinical Features

Each of the various leukodystrophies has a characteristic clinical presentation, and most can be diagnosed by genetic or biochemical methods. Despite differences in underlying mechanisms, the leukodystrophies share many features because of the common myelin target. Affected children are normal at birth but begin to miss developmental milestones during infancy and childhood. Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia. In general, the earlier the age at onset, the more severe the deficiency and clinical course.

**Table 23-2. Selected Leukodystrophies**

Metabolic Disorder	Inheritance	Abnormality
Metachromatic leukodystrophy	AR	Arylsulfatase A deficiency
Krabbe disease	AR	Galactocerebroside $\beta$ -galactosidase deficiency
Adrenoleukodystrophy	AR, X	Peroxisomal defects; elevated very long chain fatty acids
Canavan disease	AR	Aspartoacylase deficiency
Pelizaeus-Merzbacher disease	X	Mutations in proteolipid protein
Vanishing white matter disease	AR	Translation initiation factor; link to myelin unclear
Alexander disease	AR	Mutations in glial fibrillary acidic protein

AR, autosomal recessive inheritance; X, X-linked inheritance.

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### SUMMARY

**Primary Diseases of Myelin** Because of the critical role of myelin in nerve conduction, diseases of myelin can lead to widespread and severe neurologic deficits. Diseases of myelin can be grouped into *demyelinating diseases* (in which normal myelin is broken down for inappropriate reasons—often by inflammatory processes), and *dysmyelinating diseases* (which are metabolic disorders that include the leukodystrophies in which the underlying structure of the myelin is abnormal or its turnover is abnormal). Multiple sclerosis, an autoimmune demyelinating disease, is the most common disorder of myelin, affecting young adults often with a relapsing-remitting course with eventual progressive accumulation of neurologic deficits. Other less common forms of immune-mediated demyelination often follow infections and are more acute illnesses.





## ACQUIRED METABOLIC AND TOXIC DISTURBANCES

Toxic and acquired metabolic diseases are relatively common causes of neurologic illnesses. Because of the metabolic demands of the brain, it is particularly vulnerable to nutritional diseases and alterations in metabolic state. Surprisingly, even though we might expect metabolic alterations to affect the entire brain uniformly, there can be very distinct clinical presentations because of unique features or requirements of different anatomic regions. In the next section, only a few of the more common types of injury will be discussed.

### Nutritional Diseases

#### *Thiamine Deficiency*

In addition to the systemic effects of thiamine deficiency (*beriberi*), there may also be abrupt development of confusion, abnormalities in eye movement and ataxia, a syndrome termed *Wernicke encephalopathy*. The acute stages, if unrecognized and untreated, may be followed by a prolonged and largely irreversible condition, *Korsakoff syndrome*, associated with profound memory disturbances. Because the two syndromes are closely linked, the term Wernicke-Korsakoff syndrome is often applied.

The syndrome is particularly common in the setting of chronic alcoholism but may also be encountered in patients with thiamine deficiency resulting from gastric disorders, including carcinoma, chronic gastritis, or persistent vomiting. Treatment with thiamine can reverse the manifestations of Wernicke syndrome.

#### **Morphology**

Wernicke encephalopathy is characterized by foci of hemorrhage and necrosis, particularly in the mammillary bodies but also adjacent to the ventricle, especially the third and fourth ventricles. Despite the presence of necrosis, there is relative preservation of many of the neurons in these structures. Early lesions show dilated capillaries with prominent endothelial cells. Subsequently, the capillaries leak red cells into the interstitium, producing hemorrhage. As the lesions resolve, there is infiltration of macrophages and development of a cystic space with hemosiderin-laden macrophages as a permanent sign of the process. Lesions in the medial dorsal nucleus of the thalamus seem to be the best correlate of the memory disturbance in Korsakoff syndrome.

#### *Vitamin B<sub>12</sub> Deficiency*

In addition to pernicious anemia, deficiency of vitamin B<sub>12</sub> may lead to devastating neurologic deficits associated with changes in the spinal cord. This disorder involves both ascending and descending fiber bundles in the spinal cord and is responsible for its name, *subacute combined degeneration of the spinal cord*. Symptoms develop over weeks, initially with slight ataxia and numbness and tingling in the lower extremities, but can progress rapidly to include spastic weakness of the lower extremities. Complete paraplegia can also occur. With prompt vitamin replacement therapy, clinical improvement occurs; however, if complete paraplegia has developed, recovery is poor.

### Acquired Metabolic Disorders

Individuals with several systemic derangements may develop evidence of CNS dysfunction; only those associated with [glucose](#)<sup>®</sup> levels and liver dysfunction will be considered here.

.. . . .

### *Hypoglycemia*

Since the brain requires **glucose** as a substrate for its energy production, the cellular effects of diminished **glucose** resemble those of oxygen deprivation (hypoxia). The pattern of injury resembles global hypoxia, with injury particularly evident in the CA1 area of the hippocampus. One important difference, however, is that the Purkinje cells of the cerebellum are relatively spared in hypoglycemia. As with anoxia, if the level and duration of hypoglycemia are of sufficient severity, there may be widespread injury to many areas of the brain.

### *Hyperglycemia*

Hyperglycemia is most commonly found in the setting of inadequately controlled diabetes mellitus and can be associated with either ketoacidosis or hyperosmolar coma. Systemically there is dehydration; however, patients develop confusion, stupor, and eventually coma because of the mass action transport of **glucose** (insulin-independent) into neurons associated with osmotic accumulation of water. The hyperglycemia must be corrected gradually; otherwise, severe cerebral edema may follow.

### *Hepatic encephalopathy*

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Individuals with decreased hepatic function develop depressed levels of consciousness leading to coma. In the early stages patients have a characteristic "flapping" tremor (asterixis) when extending their arms with palms facing the observer. Since the liver fails to clear ammonia through the **urea** cycle, it is thought that this metabolic product causes the changes in brain function, although the absolute levels of ammonia in symptomatic patients vary widely. Potential mechanisms are diverse but include alterations in synaptic transmission as well as metabolic alterations in astrocytes as they attempt to detoxify the ammonia. The cellular response in the CNS is predominantly glial, with astrocytes in the cortex and basal ganglia developing swollen pale nuclei (called *Alzheimer type II cells*).

### **Toxic Disorders**

The list of toxins with effects on the brain is extremely long. Among the major categories of neurotoxic substances are *metals*, including lead (often causing a diffuse encephalopathy), as well as arsenic and mercury; *industrial chemicals*, including organophosphates as in pesticides and methanol (causing blindness from retinal damage); and *environmental pollutants* such as carbon monoxide (combining hypoxia with selective injury to the globus pallidus).

*Ethanol* is a drug with several different types of effects on the brain. While the acute intoxication effects of ethanol are reversible, excessive intake can result in profound metabolic disturbances, including brain swelling and death. Chronic alcohol exposure leads to cerebellar dysfunction in about 1% cases, with truncal ataxia, unsteady gait, and nystagmus. This is associated with atrophy in the anterior vermis of the cerebellum. The brain can also be affected by exposure to alcohol during development (fetal alcohol syndrome; [Chapter 7](#)).

Neurotoxic side effects have also been associated with the administration of chemotherapeutic agents for the treatment of tumors. *Methotrexate*, an important antineoplastic agent, may cause CNS injury, particularly in persons receiving intrathecal or high-dose systemic therapy in conjunction with radiation therapy. The morphologic changes associated with methotrexate toxicity are most prominent in white matter and consist of necrosis, demyelination, gliosis, and calcification.

*Ionizing radiation* can cause rapidly evolving symptoms of an intracranial mass, including headaches, nausea, vomiting, and papilledema, even after months to years after irradiation. The pathologic findings consist of large areas of coagulative necrosis in white matter with adjacent edema. Adjacent to the area of coagulative necrosis, blood vessels exhibit thickened walls with intramural fibrin-like material



were with intermediate form like material.



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## DEGENERATIVE DISEASES AND DEMENTIAS

Dementia, defined as the development of memory impairment and other cognitive deficits with pre consciousness, is emerging as one of the most important public health issues in the industrialized dementia ([Table 23-3](#)); regardless of etiology, dementia is not part of normal aging and always re

**Table 23-3. Major Causes of Dementia**

<b>Primary Neurodegenerative Disorders</b>
Alzheimer disease
Pick disease and other frontotemporal degenerations
Parkinson disease and diffuse Lewy body disease
Progressive supranuclear palsy
Huntington disease
Motor neuron disease
<b>Infections</b>
Prion-associated disorders (Creutzfeldt-Jakob disease, fatal familial insomnia, others)
HIV encephalopathy (AIDS dementia complex)
Progressive multifocal leukoencephalopathy
Miscellaneous forms of viral encephalitis
Neurosyphilis
Chronic meningitis
<b>Vascular and Traumatic Diseases</b>
Multi-infarct dementia and other chronic vascular disorders
Global hypoxic-ischemic brain injury
Chronic subdural hematomas
<b>Metabolic and Nutritional Diseases</b>
Thiamine deficiency (Wernicke-Korsakoff syndrome)
Vitamin B <sub>12</sub> deficiency
Niacin <sub>Rx</sub> deficiency (pellagra)
Endocrine diseases
<b>Miscellaneous</b>
Brain tumors
Neuronal storage diseases
Toxic injury (including mercury, lead, <a href="#">manganese<sub>Rx</sub></a> , bromides)

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

While the diseases to be discussed in this section are considered as "degenerative"-that is, reflect neurons in the brain-not all forms of dementia are degenerative.

Vascular disorders are an important cause of dementia. Patients who suffer multiple, bilateral, large infarcts during the course of months or years develop dementia, called *vascular (multi-infarct) dementia*. This disease preferentially involves large areas of the subcortical white matter with myelin and axon loss, the *disease*.

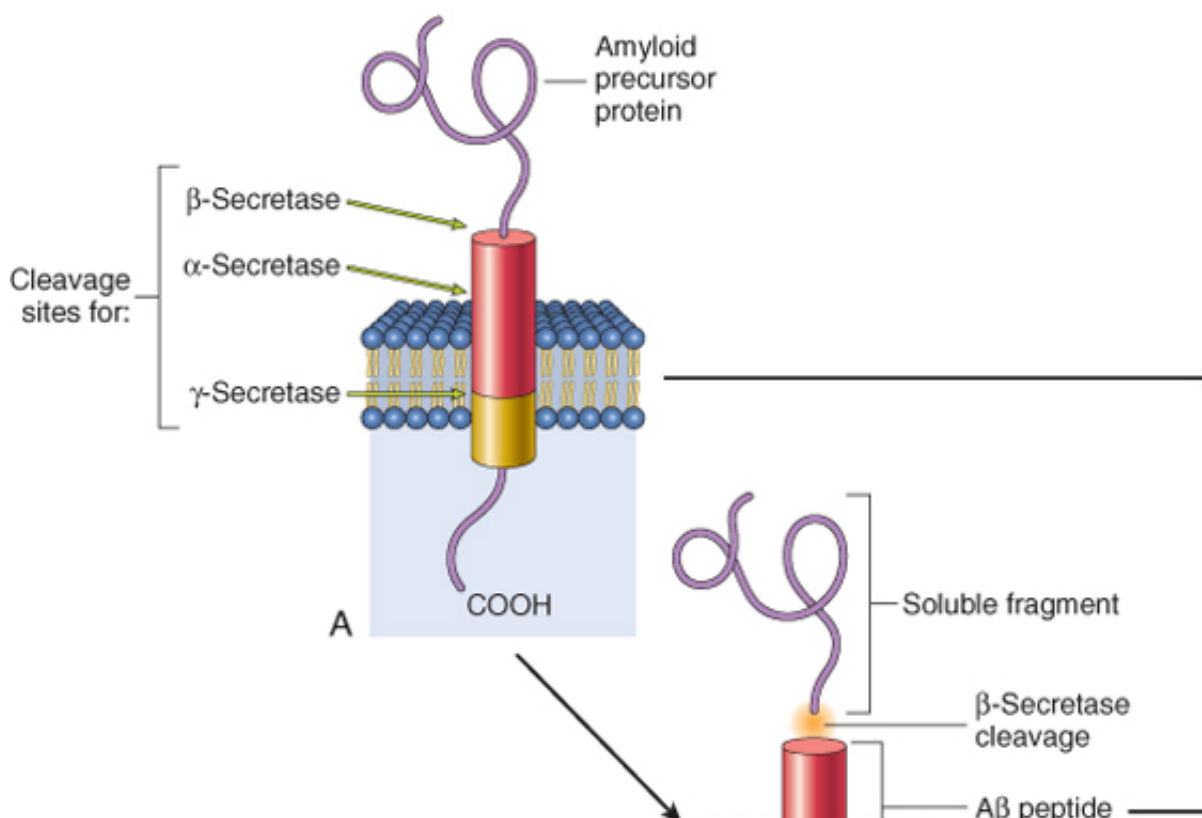
In this section, we will discuss the main causes of dementia, including Alzheimer, Parkinson, and selected disorders.

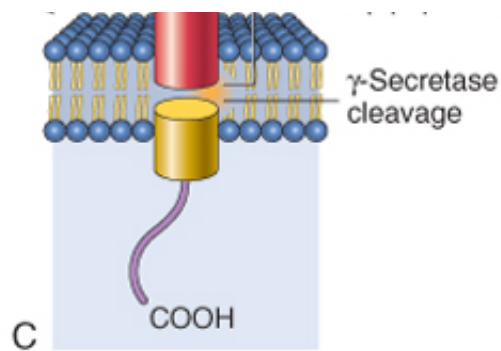
## Alzheimer Disease

Alzheimer disease is the most common cause of dementia in the elderly. The disease usually begins with impairment of higher intellectual function, with alterations in mood and behavior. Later, progressive aphasia indicates severe cortical dysfunction, and over the next 5 to 10 years, the patient becomes immobile. Death usually occurs from intercurrent pneumonia or other infections. When considered worldwide, Alzheimer disease is 3% for individuals 65 to 74 years old, 19% for 75 to 84 years, and 47% for 85 years and older. The incidence with age has given rise to major medical, social, and economic problems in countries where pathologic examination of brain tissue remains necessary for the definitive diagnosis of Alzheimer disease. Modern radiologic methods allow accurate diagnosis in 80% to 90% of cases.

Most cases are sporadic, although at least 5% to 10% are familial. In general, patients rarely become demented until late in life, but early onset can be seen with some of the heritable forms. Evidence from familial forms of the disease indicates that a peptide ( $\beta$  amyloid, or  $A\beta$ ) in the brain initiates a chain of events that result in the morphologic changes of dementia. This peptide is derived from a larger membrane protein known as amyloid precursor protein (APP) and can be cut by two enzymes,  $\alpha$ -secretase and  $\gamma$ -secretase, in a process known as non-amyloidogenic cleavage. Alternatively, APP can be cut by  $\beta$ -site APP-cleaving enzyme and  $\gamma$ -secretase to generate  $A\beta$ . Generation and accumulation of  $A\beta$  increase with advancing age. Mutations in APP or in components of  $\gamma$ -secretase (presenilin-1 or presenilin-2) lead to early onset of the disease by increasing the rate at which  $A\beta$  accumulates. Alzheimer disease occurs in almost all people who have the gene encoding APP located on chromosome 21 who survive beyond 45 years (due to APP gene dosage).

The search for genes associated with typical, sporadic Alzheimer disease is beginning to identify new clues about the pathogenesis of the disease. An allele of apolipoprotein, called  $\epsilon 4$  (ApoE4), is associated with the disease in many cases, and is thought to both increase the risk and lower the age of onset of the disease. ApoE4 is the most common allele, but how it does so is not known. Another gene, called *SORL1*, has recently been found to also be associated with the disease. Deficiency of the SORL1 protein may alter the intracellular trafficking of APP, shuttling it to lysosomes where it is degraded. If APP is generated by enzymatic cleavage, the net result being increased generation of this pathogenic peptide.





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Figure 23-28 Amyloid precursor protein (APP) is a transmembrane protein. **A**, Cellular trafficking of APP involves the endoplasmic reticulum and Golgi apparatus, with eventual expression in the cell surface. **B**, Surface APP can be cleaved through  $\alpha$ -secretase cleavage or can be reinternalized into an endosomal compartment. **C**, Generation of  $A\beta$  by  $\beta$ -secretase and other compartments.  $A\beta$  fragments form amyloid fibrils.

Accumulation of  $A\beta$  has several effects on neurons and neuronal function. Small aggregates of  $A\beta$  aggregates can be toxic to neurons and synaptic endings. Larger deposits, in the form of plaques, elicit an inflammatory response that can result in further cell injury, and may cause altered region-to-region effects on axons and dendrites. The presence of  $A\beta$  also leads neurons to hyperphosphorylate tau; this increased level of phosphorylation, tau redistributes within the neuron from the axon into dendrites and axons. This process also results in neuronal dysfunction and cell death. The anatomic distribution of  $A\beta$  deposits, in parallel, are responsible for the clinical signs and symptoms; they appear to develop well in adv

### Morphology

Macroscopic examination of the brain shows a variable degree of cortical atrophy and enlarged cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes. There is compensatory ventricular enlargement (hydrocephalus ex vacuo). At the time Alzheimer disease is diagnosed by the presence of **plaques** (a type of extracellular lesion) and **neurofibrillary tangles** (a type of intracellular lesion) (Fig. 23-29). Because these lesions are present to a lesser extent in the brains of elderly nondemented individuals, the current criteria for Alzheimer disease are based on a combination of clinical and pathologic features. There is a progression of involvement of brain regions: pathologic changes (specifically plaque-associated neuronal loss and glial reaction) are evident earliest in the entorhinal cortex, followed by the hippocampal formation and isocortex, and then extend into the neocortex. Silver immunohistochemistry is extremely helpful in assessing the true burden of these lesions.

**Neuritic plaques** are focal, spherical collections of dilated, tortuous, silver-staining (dystrophic neurites), often around a central amyloid core (Fig. 23-29). Neuritic plaques range from 10 to 200  $\mu\text{m}$  in diameter; microglial cells and reactive astrocytes are present at their periphery. They are found in the hippocampus and amygdala as well as in the neocortex, although there is relative sparing of primary motor and sensory cortices until late in the course of the disease. The core of the plaque contains  $A\beta$  (Fig. 23-29B).  $A\beta$  deposits can also be found that lack any surrounding dystrophic neurites; these are typically found in superficial portions of cerebral cortex and cerebellar cortex and may represent an early stage of plaque development.

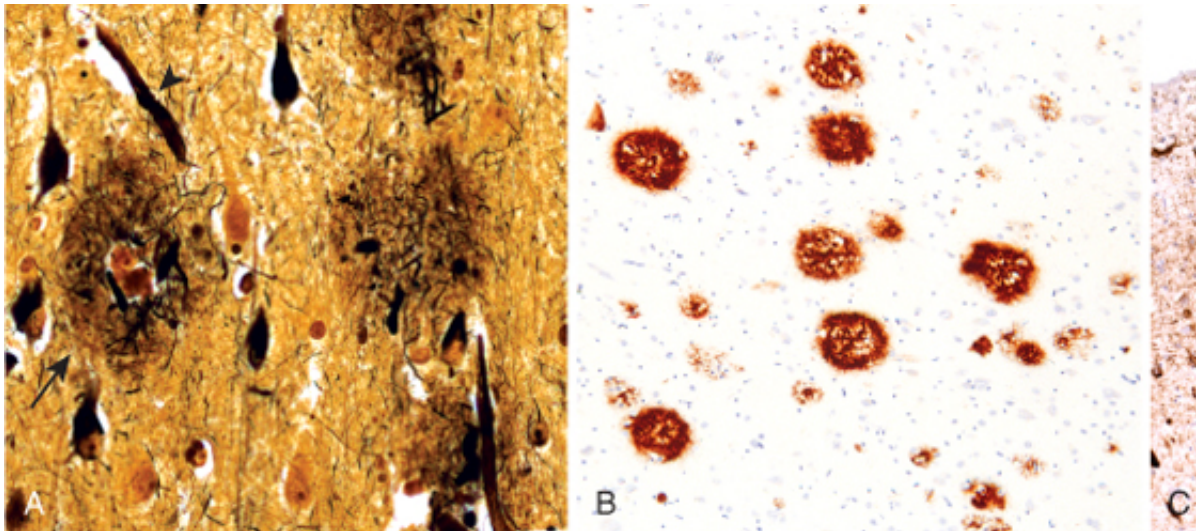
**Neurofibrillary tangles** are bundles of paired helical filaments visible as basophilic inclusions in the cytoplasm of the neurons that displace or encircle the nucleus (Fig. 23-29C); tangles form as neurons die, then becoming a form of extracellular pathology. They are commonly found in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, amygdala, the basal forebrain, and the raphe nuclei. A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau** (Fig. 23-29C). Tangles are also found in other degenerative diseases as well.



## Frontotemporal Dementia

Another major category of disease that results in dementia is called *frontotemporal dementias*; the (progressive deterioration of language and changes in personality) corresponding to degeneration of the frontal and temporal lobes. The symptoms often occur before memory disturbance, and this difference in presentation distinguishes it from Alzheimer disease on clinical grounds. Some of these dementias are caused by mutations in the tau protein that leads to neurofibrillary tangles. The basic gross finding is atrophy affecting predominantly the frontal and temporal lobes. Microscopically, the disease is defined by the presence of specific inclusions. In some cases the disease defining inclusions consist of abnormal accumulations of tau protein.

## Parkinsonism



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Figure 23-29 Alzheimer disease. **A**, Plaques (arrow) contain a central core of amyloid and a surrounding region of intracellular inclusions (Bielschowsky stain). **B**, Immunohistochemistry against A $\beta$  shows that the peptide is present in the surrounding region. **C**, Neurons containing tangles are stained by immunohistochemistry.

Parkinsonism is a clinical syndrome characterized by diminished facial expression (masked facies), bradykinesia (slowness of movement), festinating gait (progressively shortened, accelerated steps), rigidity, and a "pill-rolling" tremor. It is seen in a number of conditions that share damage to dopaminergic neurons of the substantia nigra. Parkinsonism can be induced by drugs that affect these neurons, particularly dopamine antagonists. Dopamine agonists become an important tool in animal models to develop and test new therapies. Other diseases in this category include post-encephalitic parkinsonism (associated with the influenza pandemic), multiple system atrophy, corticobasal degeneration, and some cases of Huntington disease.

*Idiopathic Parkinson disease* is the most common neurodegenerative disease associated with parkinsonism in the absence of a toxic or other known underlying etiology. It is treated with L-dihydroxyphenylalanine (L-DOPA) treatment (see below). Parkinson disease has been targeted for treatment including transplantation, gene therapy, and stem cell injection. Currently used neurosurgical approaches include placement of lesions in the extrapyramidal system to compensate for the loss of nigrostriatal function and stimulating electrodes (deep brain stimulation).

While most Parkinson disease is sporadic, there are both autosomal dominant and recessive forms. Several specific causal mutations have been identified. For example  $\alpha$ -synuclein mutations cause autosomal dominant Parkinson disease. Even in cases of Parkinson disease not caused by mutations in this gene, the Lewy body is an inclusion containing  $\alpha$ -synuclein. This is a widely expressed neuronal protein involved in signal transduction and other cellular processes. How the alterations in sequence or protein levels result in Parkinson disease has suggested that defective degradation of the protein in the lysosome is supported by the identification of two other genetic loci for Parkinson disease, which involve genes *LRRK2* and *UCHL1* (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome).

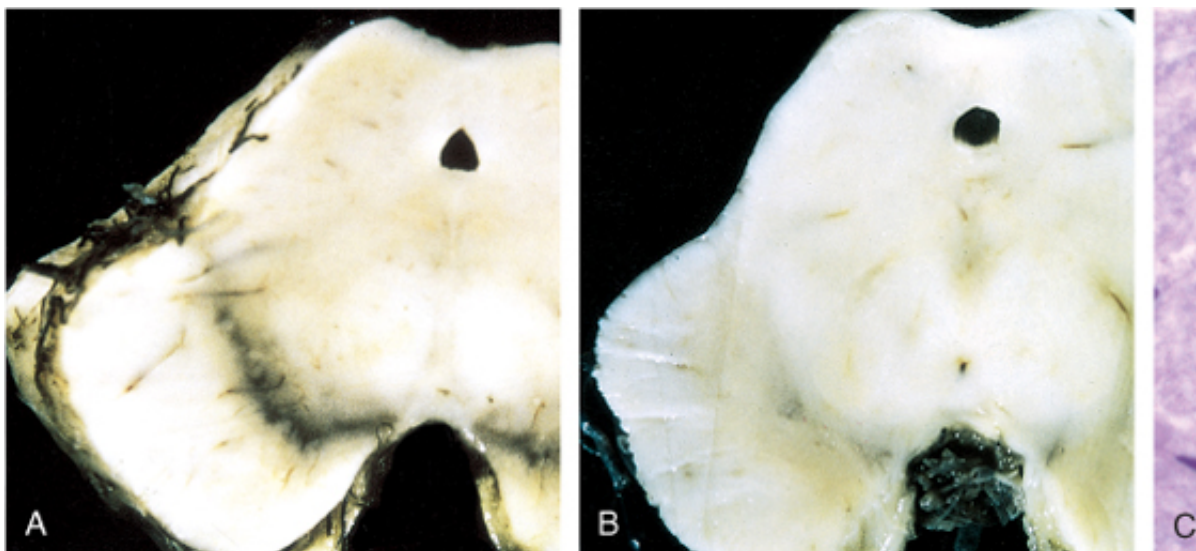
and COX II (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome).

### Morphology

On pathologic examination, the typical macroscopic findings are pallor of the substantia nigra (Fig. 23-30B) and locus ceruleus. On microscopic examination there is loss of the pigmented, neurons in these regions associated with gliosis; **Lewy bodies** (Fig. 23-30C) may be seen in the remaining neurons. These are single or multiple, intracytoplasmic, eosinophilic, round or oval inclusions that often have a dense core surrounded by a pale halo. Ultrastructurally, Lewy bodies consist of neurofilaments, densely packed in the core but loose at the rim. These filaments are composed of alpha-synuclein along with other proteins including neurofilament and ubiquitin. Lewy bodies may also be seen in cholinergic cells of the basal nucleus of Meynert, as well as in other brain-stem nuclei. Distinct inclusions are also found in cerebral cortical neurons, especially in the cingulate and parahippocampal gyrus. The presence of Lewy bodies in limbic and neocortical structures is associated with cognitive impairment-the disorder recognized as dementia with Lewy bodies, discussed in Chapter 24.

### Clinical Features

L-DOPA therapy is often extremely effective in symptomatic treatment, but it does not significantly alter the course of the disease. Over time, L-DOPA becomes less effective at providing the patient with symptomatic relief, and the patient may require motor function on its own. The disease usually progresses over 10 to 15 years, with eventual severe disability and immobility. Death is usually the result of intercurrent infection or trauma from frequent falls caused by rigidity.



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Figure 23-30 Parkinson disease. **A**, Normal substantia nigra. **B**, Depigmented substantia nigra in idiopathic Parkinson disease. **C**, Microscopic view of a substantia nigra neuron with a prominent eosinophilic inclusion body (arrowhead).

About 10% to 15% of individuals with Parkinson disease develop dementia, with the incidence increasing with age. Characteristic features of this disorder include a fluctuating course and hallucinations. While many cases resemble evidence of Alzheimer disease, the dementia in other Parkinson disease patients is attributed to involvement of the cerebral cortex.

### Huntington Disease

Huntington disease (HD) is an inherited autosomal dominant disease characterized clinically by progressive motor dysfunction, dementia, and psychiatric symptoms. The movement disorder consists of chorea (dystonic movements) affecting all parts of the body; patients may develop parkinsonism as well. The disease is relentlessly progressive, resulting in death after an average course of about 15 years.

All individuals with *HD* have the same type of mutation—a trinucleotide repeat expansion in a gene protein (huntingtin). There is a polymorphic CAG trinucleotide repeat in the gene, encoding a polyalleles contain 11 to 34 copies of the repeat; in disease-causing alleles the number of repeats is increased. There is strong genotype-phenotype correlation in the sense that the larger the number of repeats, the earlier the symptoms begin. Once the symptoms begin, however, the course of the illness is not significantly dependent on repeat length.

Repeat expansions occur during spermatogenesis, and paternal transmission is associated with a higher frequency of expansion. Expanding mutations are uncommon, and most apparently "sporadic" cases can be related to expansion in a parent before expression of the disease. Some unaffected fathers have expanded repeats that expand in their children. The identification of individuals in the presymptomatic phase of their disease is of great burden and should not be undertaken in the absence of appropriate counseling.

It remains unclear how the huntingtin protein with an expanded polyglutamine tract causes disease. The mutant huntingtin with expanded polyglutamine stretches binds to and sequesters various transcription factors and other critical proteins. An alternative, and not exclusive, possibility is that the mutant huntingtin causes functional abnormalities which lead to neurodegeneration. Some of these functional abnormalities may, in fact, result from abnormalities in proteins involved in mitochondrial electron transport and anti-oxidant proteins. The protein is widely distributed in the brain, but it is also unclear why there is such restricted involvement of brain areas. Abnormal huntingtin is able to be observed in tissue. It is possible that the abnormal protein fails to fold properly, and accumulates in some neurons. However, this mechanism of pathogenesis has not been formally proved.

### **Morphology**

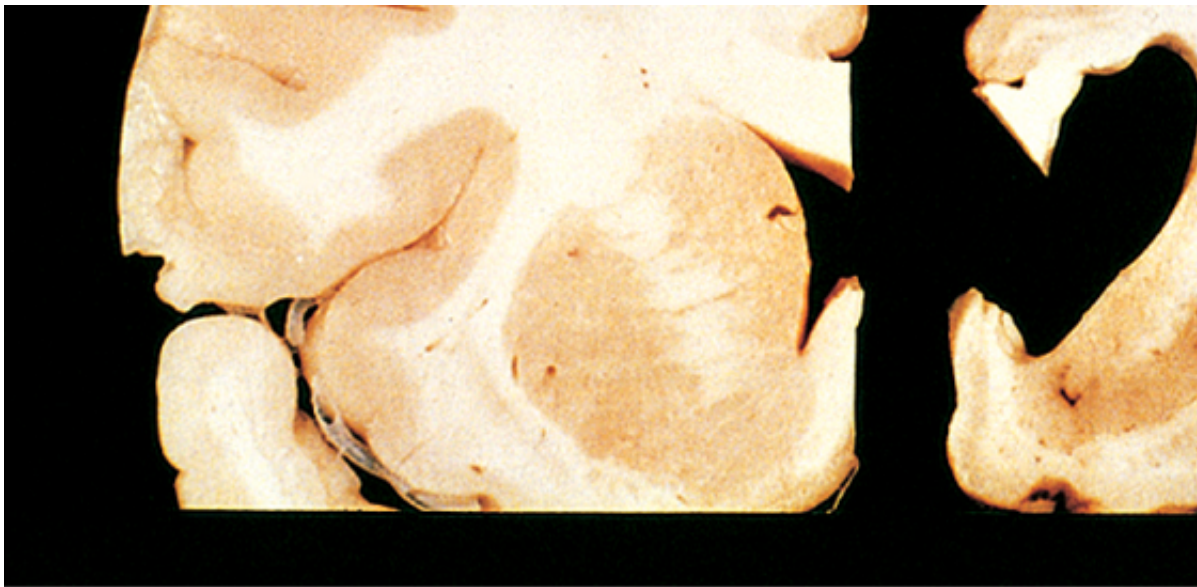
On gross examination, the brain is small and shows striking atrophy of the caudate nucleus and, less dramatically, the putamen (Fig. 23-31). Pathologic changes develop over the years, progressing from medial to lateral direction in the caudate and from dorsal to ventral in the putamen. The lateral ventricle is atrophied secondarily, and the lateral and third ventricles are dilated. Atrophy is most marked in the frontal lobe, less often in the parietal lobe, and occasionally in the entire cortex.

On microscopic examination there is severe loss of neurons from these regions of the basal ganglia. The loss of small neurons generally precedes that of the larger. The medium-sized, spiny neurons that use gamma-aminobutyric acid as their neurotransmitter, along with enkephalin, dynorphin, and substance P, are especially affected. There is also fibrillary gliosis that is more extensive than in the normal brain. There is a direct relationship between the degree of degeneration in the striatum and the severity of motor symptoms; a similar but less strong relationship exists between cortical neuron loss and cognitive symptoms. In the remaining striatal neurons and in the cortex, there are intranuclear inclusions that contain ubiquitinated huntingtin protein.

### **Clinical Features**







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Figure 23-31 Huntington disease. Normal hemisphere on the left compared with the hemisphere with Huntington disease showing caudate head enlargement, striatum and ventricular dilation. (Courtesy of Dr. J.P. Vonsattel, Columbia University, N

The age at onset is most commonly in the fourth and fifth decades and is related to the length of the CAG repeat. If the number of repeats exceeds 70 copies, the disease can present in adolescence or even earlier, so-called juvenile HD. Juvenile HD is characterized by prominent motor symptoms, with cognitive impairment. The movement disorder of HD is choreiform, with increased and involuntary writhing movements of the extremities are typical. Early symptoms of higher cortical dysfunction include personality changes, affective disorders, and there may be progression to a severe dementia. HD patients have an increased risk of infection being the most common natural cause of death.

### Spinocerebellar Degenerations

This is a clinically heterogeneous group of illnesses that include several distinct diseases; these diseases have different patterns of inheritance, age at onset, and constellation of signs and symptoms. This group of diseases affects the cerebellar cortex, spinal cord, other brain regions, and peripheral nerves. Because of this pattern of involvement, these diseases include a combination of cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy. The pattern of involvement without distinctive histopathologic changes, occurs in the affected areas and is associated with mitochondrial dysfunction.

Among the many forms of spinocerebellar ataxias (known in general as SCAs), there are several forms caused by expansion of a CAG repeat encoding a polyglutamine tract similar to Huntington disease. In these forms, inclusions containing the abnormal protein can be found, and there is a correlation between the size of the repeat and the age at onset. Other SCAs are caused by nucleotide repeat expansions in untranslated regions.

*Friedreich ataxia* is an autosomal recessive progressive illness, generally beginning in the first decade of life with gait ataxia, hand clumsiness and dysarthria. Deep tendon reflexes are depressed or absent, and an extensor plantar response is present. Joint position and vibratory sense are impaired, and there is sometimes loss of pain and temperature sensation. Most patients develop pes cavus and kyphoscoliosis. There is a high incidence of cardiac disease, and many patients become wheelchair bound within 5 years of onset; the cause of death is intercurrent pulmonary infections. The disease is caused by a GAA trinucleotide repeat expansion in a gene for a protein that is involved in determining iron metabolism. The expansion causes a change in the structure of the protein but rather leads to extremely low levels of the protein.

### Diseases of Motor Neurons

These are a series of diseases that affect the lower motor neurons in the spinal cord and brain stem. The loss of lower motor neurons results in denervation of muscular targets with wasting and fasciculations. Loss of the projection of upper motor neurons onto the lower motor neurons results in spastic paralysis. The diseases are grouped into two main categories: "upper motor neuron" and "lower motor neuron" diseases.



and positive Babinski sign. Sensory systems and cognitive functions are usually unaffected, but type 1 is associated with cognitive impairment. **Amyotrophic Lateral Sclerosis (Motor Neuron Disease; Lou Gehrig's Disease)**

This is the most common form of neurodegeneration affecting the motor system. It is characterized by hyper-reflexia due to loss of both upper and lower motor neurons. The "lateral sclerosis" refers to the tracts in the lateral portion of the spinal cord, as a result of loss of upper motor neurons.

The disease affects men slightly more frequently than women and becomes clinically manifest in late middle age. About 10% are sporadic, 5% to 10% are familial, mostly with autosomal dominant inheritance. The best understood form is linked to chromosome 21, involving the gene encoding a form of superoxide dismutase, SOD1. Mutations in this gene are found in the familial cases of amyotrophic lateral sclerosis. A wide variety of missense mutations have been found, each with an adverse gain-of-function phenotype. As with huntingtin, the mutation may cause misfolding of the protein.

### **Morphology**

Grossly, the most evident changes are found in anterior roots of the spinal cord, which become thin and pale (rather than white). In especially severe cases, the precentral gyrus (motor cortex) is also atrophic. Microscopic examination demonstrates a reduction in the number of anterior horn cells throughout the length of the spinal cord associated with reactive gliosis and loss of myelin. Similar findings are found with involvement of motor cranial nerve nuclei, notably the nuclei of the extraocular muscles. Death of upper motor neurons—a finding that may be hard to detect on gross examination—results in degeneration of the descending corticospinal tracts, which are seen in the spinal cord. With the loss of innervation from the death of anterior horn cells, the lower motor neurons show neurogenic atrophy.

### **Clinical Features**

Early symptoms include asymmetric weakness of the hands, manifested by dropping objects and cramping and spasticity of the arms and legs. As the disease progresses, muscle strength and bulk of individual motor units, termed *fasciculations*, occur. The disease eventually involves the respiratory muscles, leading to pulmonary infection, which are the usual cause of death. The severity of involvement of the upper and lower motor neurons varies, although most patients have involvement at both levels. Familial cases develop symptoms earlier. The average clinical course is comparable with roughly a 50% 5-year survival. In some patients, degeneration of the cranial nerve nuclei occurs early and progresses rapidly, a pattern of disease referred to as *bulbar amyotrophic lateral sclerosis*. In these cases, abnormalities of swallowing and speaking dominate.

### **Bulbospinal Atrophy (Kennedy Disease)**

This X-linked adult-onset disease affecting lower motor neurons is characterized by distal limb atrophy, dysphagia and atrophy and fasciculations of the tongue. Affected individuals manifest androgen insensitivity, testicular atrophy, and oligospermia. This is a trinucleotide-repeat disorder, similar to Huntington disease; in this case, the repeat is in the coding region of the androgen receptor.

### **Spinal Muscular Atrophy**

These are a distinctive group of autosomal recessive motor neuron diseases that begin in childhood. They are characterized by weakness and wasting of motor neurons and weakness associated with muscle fiber atrophy that often involves entire fasciculi. The most common form of spinal muscular atrophy, SMA1 (Werdnig-Hoffmann disease), has its onset at birth and usually leads to death within the first 3 years of life. All forms of the disease are associated with mutations in the SMN gene on chromosome 5.

## **SUMMARY**

**Degenerative Diseases** Neurodegenerative diseases cause symptoms that result from the involvement of the brain. Diseases that affect the cerebral cortex primarily (e.g., Alzheimer disease) are more likely to cause cognitive change, alterations in personality, and memory impairment. Accumulation of the Aβ peptide, derived from amyloid precursor protein, is characteristic of Alzheimer disease. Diseases that affect basal ganglia (e.g., Huntington or Parkinson disease) cause motor symptoms as prominent clinical features. Parkinson disease is caused by loss of dopamine-producing neurons, and Huntington disease is caused by trinucleotide repeat expansion in the huntingtin gene.

neurons, and Huntington disease is caused by trinucleotide repeat expansion of the huntingtin gene, resulting in disease-causing gain of function. Diseases that affect the cerebellum (e.g., SCA) manifest as ataxia, along with other symptoms. Diseases that affect upper motor neurons (e.g., amyotrophic lateral sclerosis) will present with weakness as the primary symptom. All of these diseases are associated with abnormal aggregation of proteins, which can interfere with normal function or may trigger apoptosis. Familial forms of these diseases are associated with mutations in the genes encoding these proteins.



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## DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system begins a few millimeters from the pial surface of the brain and spirally replace oligodendroglial processes as the source of myelin. In the peripheral nervous system myelin is different from CNS myelin but also contains several proteins that are unique to the periphery. Abnormalities in these proteins have been implicated in the development of certain hereditary peripheral nerve disorders. Myelinated axons are covered by concentric laminations of Schwann cell cytoplasm. The myelin sheath contributed by each Schwann cell and the space between adjacent internodes is termed the *node of Ranvier*. Each myelin internode is formed by a single Schwann cell. The normal peripheral nerve also contains many smaller-diameter unmyelinated axons, which are covered by the cytoplasm of a single Schwann cell. Groups of myelinated and unmyelinated axons, in turn, are covered by concentrically arrayed *perineurial cells*. Axons are insulated from the interstitial fluids of the body by a barrier analogous to the blood-brain barrier, formed by tight junctions between endothelial cells in small blood vessels and tight junctions between adjacent perineurial cells. Disorders of the peripheral nervous system include those arising from Schwann cells and other nerve sheath elements.

### Patterns of Nerve Injury

A variety of disease processes can affect nerves (Table 23-4). In general, there are two main patterns of nerve injury based on the target of the insult: either the Schwann cell or the axon. Diseases that affect primarily the myelin, referred to as *segmental demyelination*. In contrast, primary involvement of the neuron and its axon is called *axonal degeneration*. In some diseases, axonal degeneration may be followed by *axonal regeneration*.

#### Segmental Demyelination

Segmental demyelination occurs when there is dysfunction or death of the Schwann cell or damage to the myelin sheath, either as a primary abnormality of the axon. The process affects some Schwann cells, and their corresponding myelin segments (Fig. 23-32). The disintegrating myelin is engulfed initially by Schwann cells and later by macrophages. In some cases, remyelination occurs, with a population of cells within the endoneurium differentiating to replace injured myelin and encircle the axon and, in time, remyelinate the denuded portion. Remyelinated internodes, however, are thinner myelin in proportion to the diameter of the axon than normal internodes.

With repetitive cycles of demyelination and remyelination, there is an accumulation of tiers of Schwann cell cytoplasm and redundant basement membrane around the axon (*onion bulbs*) (Fig. 23-33). In time, many chronic demyelinating neuropathies give way to axonal degeneration.

**Table 23-4. Causes and Types of Peripheral Neuropathies**

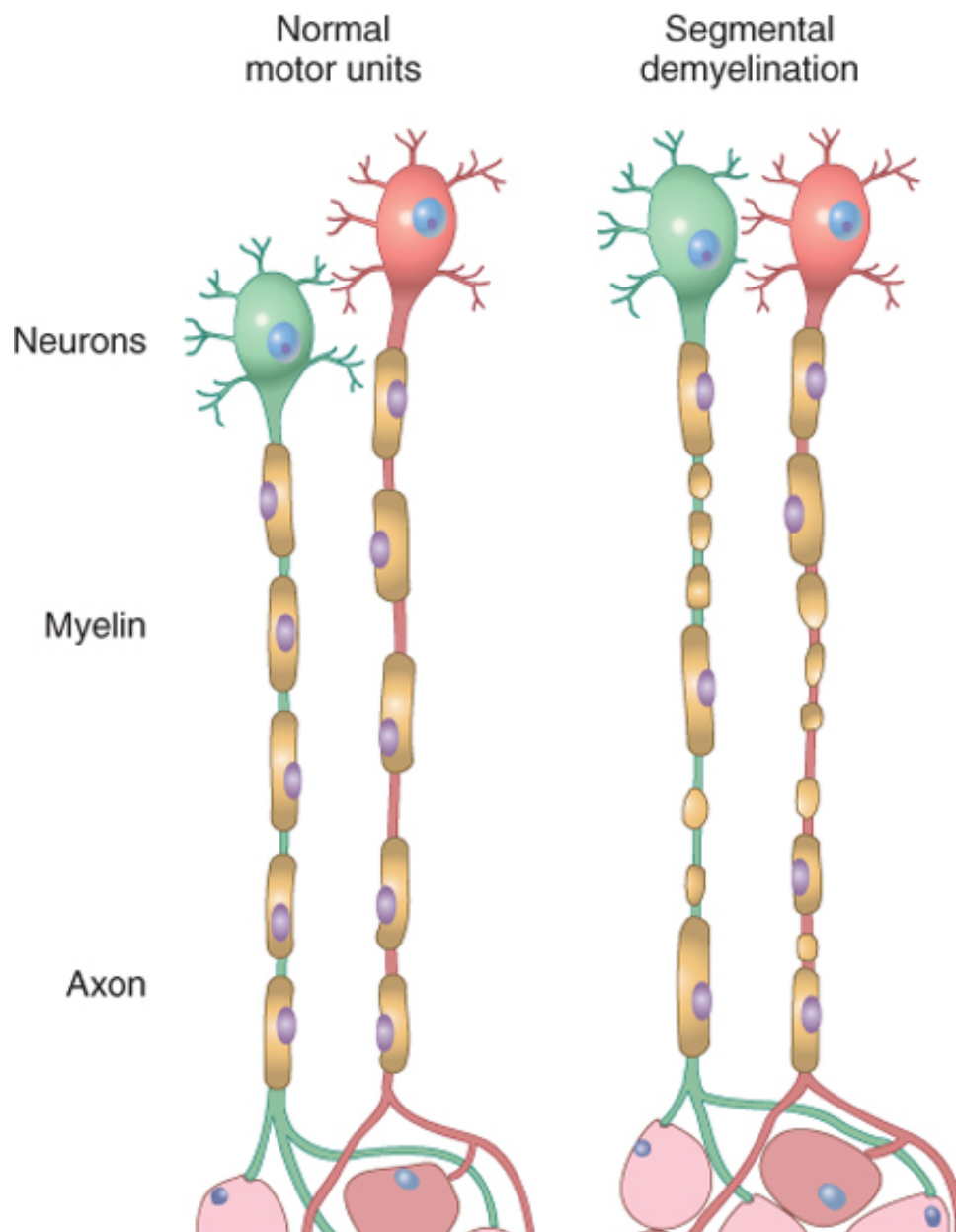
<b>Nutritional and Metabolic Neuropathies</b>
Diabetes, thiamine deficiency, pyridoxine deficiency, alcoholism, renal failure
<b>Toxic Neuropathies</b>
Lead, arsenic, cisplatin <sup>Rx</sup> , vincristine, organic solvents
<b>Inflammatory Neuropathies</b>
Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, vasculitic neuropathy, leprosy, sarcoidosis
<b>Hereditary Neuropathies</b>
Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth disease, Refsum disease, Dejerine-Sott disease), leukodystrophies
<b>Miscellaneous</b>
Amyloid neuropathy, paraneoplastic neuropathies, neuropathies associated with immunoglobulin abnormalities

#### Axonal Degeneration

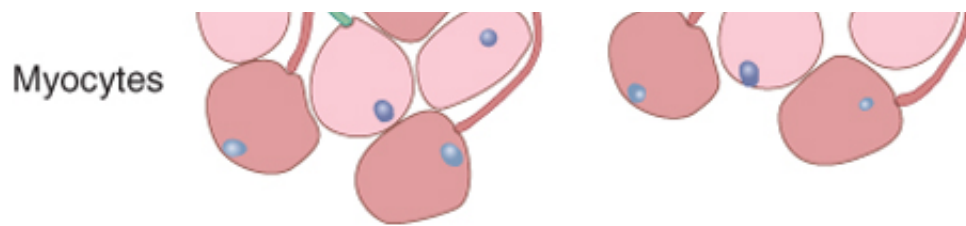
Axonal degeneration is the result of primary destruction of the axon, with secondary disintegration of the myelin sheath.

Axonal degeneration is the result of primary destruction of the axon, with secondary demyelination. It may be due either to a focal event occurring at some point along the length of the nerve (such as a generalized abnormality affecting the neuron cell body (*neuronopathy*) or its axon (*axonopathy*)). Within a day, the axon breaks down, and Schwann cells begin to degrade the myelin and then engulf the myelin compartments (*myelin ovoids*). Macrophages are recruited into the area and participate in the phagocytosis of debris. In the slowly evolving neuronopathies or axonopathies, evidence of myelin breakdown is seen in the distal portion of the fiber. The stump of the proximal portion of the severed nerve shows degenerating at any given time. The stump of the proximal portion of the severed nerve shows the most distal two or three internodes and then undergoes regenerative activity.

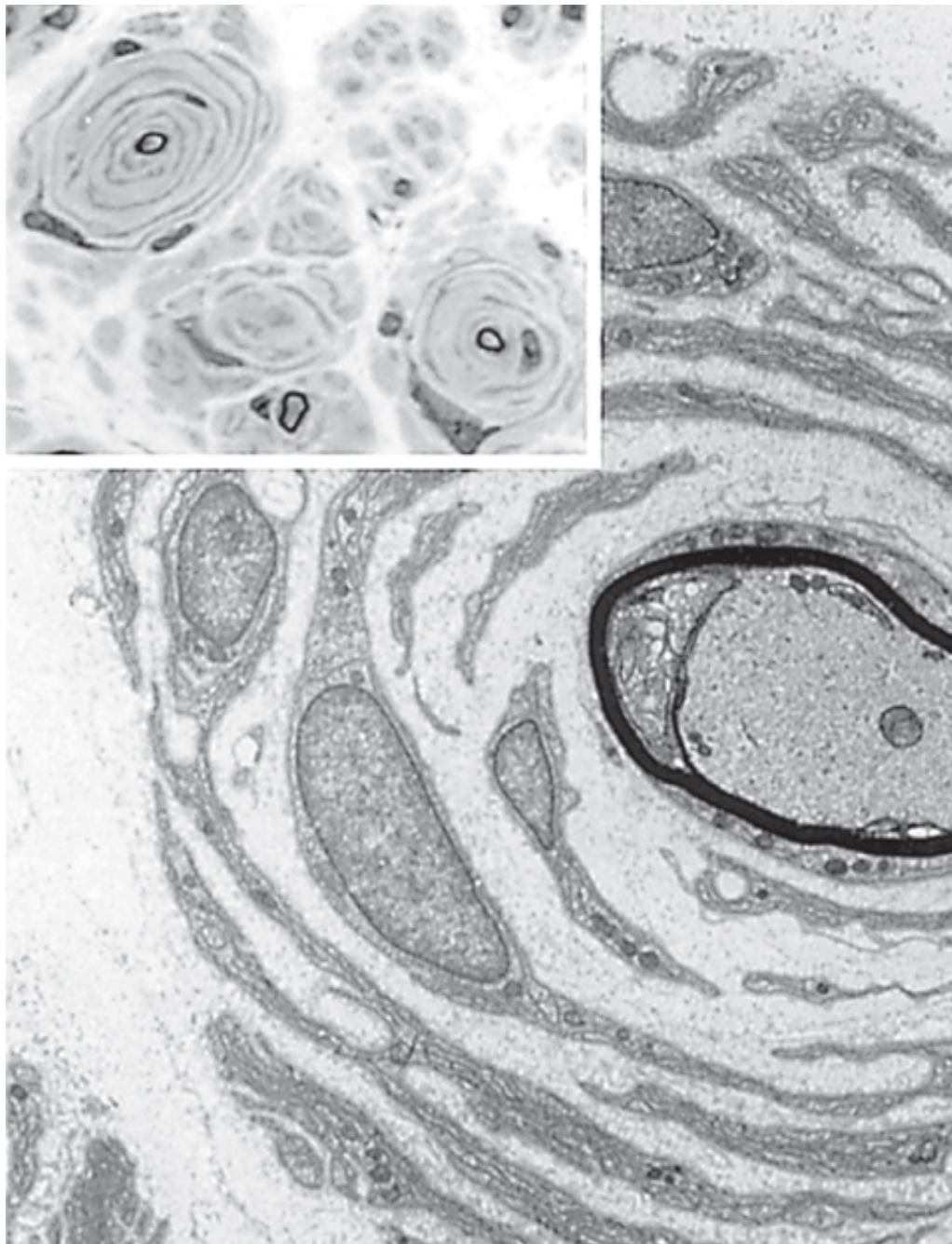
The proximal stumps of degenerated axons can develop new growth cones as the axon regrows. Schwann cells vacated by the degenerated axons to guide them, if properly aligned with the distal stump, closely aggregated thinly myelinated small-caliber axons is evidence of regeneration (*regeneration*). The process, on the order of 1 to 2 mm per day, apparently limited by the rate of the slow component (microtubulin, actin, and intermediate filaments). Despite its slow pace, axonal regeneration accounts for recovery following peripheral axonal injury.

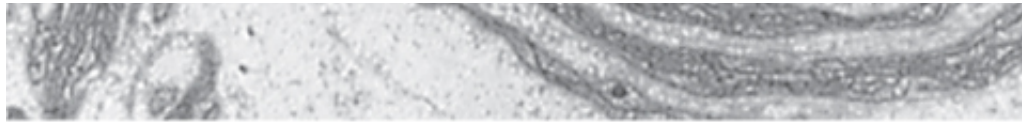






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 Figure 23-32 Normal and abnormal motor units. *Normal motor units*: Two adjacent motor units are shown. *Segmental axons* are injured and are remyelinated by multiple Schwann cells, while the axon and myocytes remain intact. *Axonal degeneration* undergo anterograde degeneration (shown for the *green neuron*), with resulting denervation atrophy c





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Figure 23-33 Electron micrograph of a single, thinly myelinated axon (arrow) surrounded by concentrically arranged myelin lamellae, characteristic of an onion bulb neuropathy. Light microscopic appearance of an onion bulb neuropathy, characterized by "onion bulbs" surrounding axons. (From Robbins Basic Pathology, 8th ed, A Text-Atlas. New York, Igaku-Shoin Medical Publishers, 2000, p. 98)

### Guillain-Barré Syndrome

This is one of the most common life-threatening diseases of the peripheral nervous system. It may be preceded by a systemic infection (usually viral) or other stress. Patients with Guillain-Barré syndrome present with weakness that may lead to death from failure of respiratory muscles. Sensory involvement is usually mild. The dominant histopathologic findings are segmental demyelination along with scant infiltrates of macrophages and reactive lymphocytes. The CSF usually contains increased levels of protein but normal cell counts. In those cases with infectious antecedents, an immunologic basis is considered most likely; treatment with intravenous immunoglobulin, which can shorten the course of the disease. With supportive care, recovery is usually complete over time.

### Neoplasms of the Peripheral Nervous System

These tumors arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, and nerve fibers. In the brain, cell characteristics, including the presence of S-100 antigen as well as the potential for melanocytic differentiation. In the spinal cord, there is a transition between myelination by oligodendrocytes and myelination by Schwann cells. In the peripheral nerve, several millimeters of the substance of the brain; thus, in addition to arising along the peripheral nerve, they may also arise within the confines of the dura. When they do this, they may cause changes in adjacent brain or spinal cord.

#### Schwannoma

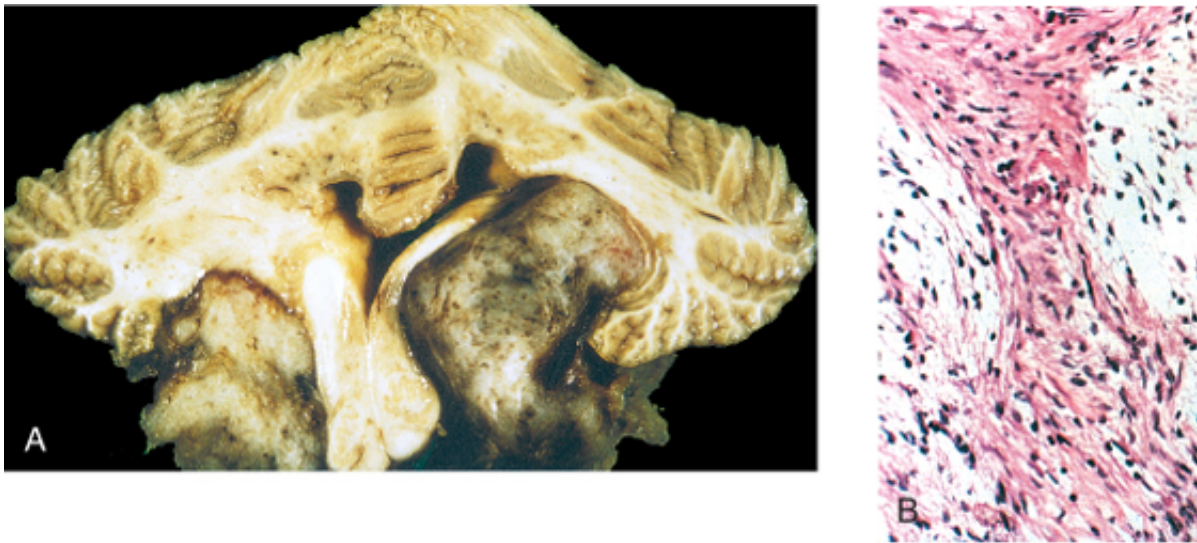
These are benign tumors arising from Schwann cells. Symptoms are referable to local compressive effects on adjacent structures (such as brain stem or spinal cord). They are often encountered in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve (Fig. 23-34). They cause tinnitus and hearing loss, and the tumor is often referred to as an acoustic neuroma, although schwannoma. Elsewhere within the dura, sensory nerves are preferentially involved, including cranial nerves. When extradural, schwannomas are most commonly found in association with large nerve trunks. Sensory and motor modalities are intermixed. Sporadic schwannomas are associated with mutations in the *NF2* gene.

#### Morphology

Schwannomas are well-circumscribed encapsulated masses that are attached to the nerve but are not separated from it. Tumors form firm, gray masses but may also have areas of cystic degeneration. On microscopic examination, tumors show a mixture of two growth patterns: Antoni A pattern of growth, elongated cells with cytoplasmic processes are arranged in a palisading pattern with moderate to high cellularity with little stromal matrix; the "nuclear-free zones" of palisading are termed Verocay bodies. In the Antoni B pattern, the tumor is less densely cellular with a loose meshwork of cells along with microcysts and myxoid areas. The cytology of the individual cells is similar, with elongated cell cytoplasm and nuclei. Because the lesion displaces the nerve of origin as it grows, axons are largely excluded from the tumor. These tumors are usually uniformly immunoreactive for S-100 protein.

#### Neurofibroma

The most common form of neurofibroma occurs in the skin (*cutaneous neurofibroma*) or in peripheral nerves (*peripheral neurofibroma*). They arise sporadically or in association with type 1 neurofibromatosis (NF1; see below). The skin lesions are small, raised, and often associated with overlying hyperpigmentation; they may grow to be large and become pedunculated. The risk of malignant transformation of these tumors is extremely small, and cosmetic concerns are their major morbidity.



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 Figure 23-34 Schwannoma. **A**, Bilateral eighth-nerve schwannomas. **B**, Tumor showing cellular areas (Antoni A), looser, myxoid regions (Antoni B areas, center). (**A**, Courtesy of Dr. K.M.

The second type is the *plexiform neurofibroma*, mostly arising in individuals with NF1. Of major concern is the difficulty in surgical removal of these plexiform tumors when they involve major nerve trunks and undergo malignant transformation.

### Morphology

**Cutaneous neurofibroma.** Present in the dermis and subcutaneous fat, these well-circumscribed, unencapsulated masses are composed of spindle cells. Although they are not invasive, they sometimes are sometimes enwrapped by the edges of the lesion. The stroma of the lesion is collagenized and contains little myxoid material. Lesions within peripheral nerves have a different appearance.

**Plexiform neurofibroma.** These tumors may arise anywhere along a nerve, although the most common site is the brachial plexus. They are frequently multiple. At the site of each lesion, the nerve is expanded, as each of its fascicles is infiltrated by the neoplasm. Unlike the case with schwannomas, it is not possible to separate the lesion from the nerve. The proximal and distal extremes of the lesion have poorly defined margins, as fingers of tumor and individual cells insert themselves between the nerve fascicles. On microscopic examination, the lesion has a loose, myxoid background with a low cellularity. Cell types present include Schwann cells with typical elongated nuclei and scant cytoplasm, larger multipolar fibroblastic cells, and a sprinkling of inflammatory cells.

### Malignant Peripheral Nerve Sheath Tumor

These are highly malignant sarcomas that are locally invasive, frequently leading to multiple recurrences. Despite their name, these tumors do not arise from malignant transformation of schwannomas. In some cases, they arise from malignant transformation of a plexiform neurofibroma. These tumors can also occur after radiation therapy.

### Morphology

The lesions are poorly defined tumor masses with frequent infiltration along the axons, as well as invasion of adjacent soft tissues. Necrosis is commonly present. A wide range of cell types may be encountered; often, the tumor cells resemble Schwann cells, with elongate nuclei and bipolar processes. Fascicle formation may be present. Mitoses, necrosis, and extreme cellular pleomorphism are common. Some but not all malignant peripheral nerve sheath tumors are immunoreactive for S-100 protein.









## FAMILIAL TUMOR SYNDROMES

Several inherited syndromes are associated with an increased risk of particular types of tumors. Those discussed here are inherited diseases characterized by the development of hamartomas and neoplasms throughout the body with particular involvement of the nervous system. Because of the combination of cutaneous manifestations and nervous system involvement, these disorders have been grouped in the past under the term "neurophakomatoses." Most of these syndromes are linked to loss of tumor suppressor genes. Symptoms are referable in part to the location of hamartomas or neoplasms; developmental delay and seizure disorders may contribute to disability in some affected individuals.

### Type 1 Neurofibromatosis

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This autosomal dominant disorder is characterized by neurofibromas (plexiform and solitary), gliomas of the optic nerve, pigmented nodules of the iris (*Lisch nodules*), and cutaneous hyperpigmented macules (*café au lait spots*). It is one of the more common genetic disorders, having a frequency of 1 in 3000. Individuals with NF1 have a propensity for the neurofibromas to undergo malignant transformation at a higher rate than that observed for comparable tumors in the general population. This is especially true for plexiform neurofibromas. The *NF1* gene is a tumor suppressor gene. The product of the gene is believed to be involved in G-protein-dependent signal transduction pathways ([Chapter 6](#)), but how *NF1* mutations lead to tumor development is unknown. The course of the disease is highly variable and independent of the particular mutation, with some individuals carrying a mutated gene and having no symptoms, while others develop progressive disease with spinal deformities, disfiguring lesions, and compression of vital structures, including the spinal cord.

### Type 2 Neurofibromatosis

This is an autosomal dominant disorder in which patients develop a range of tumors, most commonly bilateral vestibular (acoustic) schwannomas and multiple meningiomas. Gliomas, typically ependymomas of the spinal cord, also occur in these patients. Individuals with NF2 may also have non-neoplastic lesions within the nervous system where Schwann cells or glial cells are present in small collections in inappropriate places.

This disorder is much less common than NF1, having a frequency of 1 in 40,000 to 50,000. Unlike NF1, in NF2 there is some correlation between the type of mutation and clinical symptoms, with nonsense mutations usually causing a more severe phenotype than missense mutations. As mentioned previously, the *NF2* gene is commonly mutated in sporadic meningiomas and schwannomas as well.

### Tuberous Sclerosis

Tuberous sclerosis is an autosomal dominant syndrome characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Hamartomas within the CNS occur as cortical tubers and subependymal hamartomas. Seizures, which can be difficult to control with antiepileptic drugs, are associated with the cortical lesion. Extracerebral lesions include renal angiomyolipomas, retinal glial hamartomas, and pulmonary lesions and cardiac rhabdomyomas. Cysts may be found at various sites, including the liver, kidneys, and pancreas. Cutaneous lesions include angiofibromas, leathery thickenings in localized patches (shagreen patches), hypopigmented areas (ash-leaf patches), and subungual fibromas. Tuberous sclerosis results from disruption of the tumor suppressor genes *TSC1*, which encodes hamartin, or *TSC2*, which encodes tuberin. These two proteins form dimers that

regulate signaling pathways involved in protein synthesis and cell proliferation. Abnormalities of the proteins may alter neuronal proliferation, differentiation, and migration.

### **Morphology**

Cortical hamartomas of tuberous sclerosis are firm areas of the cortex that, in contrast to the softer adjacent cortex, have been likened to potatoes, hence the appellation "tubers." These hamartomas are composed of haphazardly arranged neurons that lack the normal laminar organization of the cortex. These large cells may express a mixture of glial and neuronal features, having large vesicular nuclei with nucleoli, resembling neurons, and abundant eosinophilic cytoplasm like gemistocytic astrocytes. Similar hamartomatous features are present in the subependymal nodules, where the large astrocyte-like cells cluster beneath the ventricular surface.

### **von Hippel-Lindau Disease**

This is an autosomal dominant inherited disease in which affected individuals develop hemangioblastomas within the cerebellar hemispheres, retina, and less commonly the brain stem and spinal cord. Patients may also have cysts involving the pancreas, liver, and kidneys and have a high propensity to develop renal cell carcinoma of the kidney. The disease frequency is 1 in 30,000 to 40,000. Therapy is directed at the symptomatic neoplasms, including resection of the cerebellar hemangioblastomas and laser therapy for retinal hemangioblastomas. Missense mutations in the tumor-suppressor gene *VHL* result in adrenal pheochromocytoma as well as hemangioblastoma. The VHL protein controls angiogenesis, especially in response to hypoxia ([Chapter 6](#)).

### **Morphology**

The cerebellar capillary hemangioblastoma, the principal neurologic manifestation of the disease, is a highly vascular neoplasm that occurs as a mural nodule associated with a large, fluid-filled cyst. On microscopic examination, the lesion consists of variable proportions of capillary-size or somewhat larger thin-walled vessels with intervening stromal cells, with vacuolated, lightly PAS-positive, lipid-rich cytoplasm.

### **SUMMARY**

**Neoplasms of the Peripheral Nervous System and Familial Tumor Syndromes** Neoplasms of the peripheral nervous system may originate from Schwann cells, perineurial cells and fibroblasts. They include schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor. Familial tumor syndromes include neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau disease. Genetic defects have been identified for each of these syndromes: *NF1* and *NF2* genes in neurofibromatosis, *TSC1* and *TSC2* genes in tuberous sclerosis, and defects in the *VHL* gene in von-Hippel Lindau disease.

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### Morphology

At the earliest stages, only a scant neutrophilic exudate may be found throughout the mucosa, submucosa, and muscularis propria. Subserosal vessels are congested, and often there is a modest perivascular neutrophilic infiltrate. The inflammatory reaction transforms the normal glistening serosa into a dull, granular, red membrane; this transformation signifies **early acute appendicitis** for the operating surgeon. At a later stage, a prominent neutrophilic exudate generates a fibrinopurulent reaction over the serosa (Fig. 15-46). As the inflammatory process worsens, there is abscess formation within the wall, along with ulcerations and foci of necrosis in the mucosa. This state constitutes **acute suppurative appendicitis**. Further appendiceal compromise leads to large areas of hemorrhagic green ulceration of the mucosa, and green-black gangrenous necrosis through the wall extending to the serosa, creating **acute gangrenous appendicitis** that is quickly followed by rupture and suppurative peritonitis.

**The histologic criterion for the diagnosis of acute appendicitis is neutrophilic infiltration of the muscularis propria.** Usually, neutrophils and ulcerations are also present within the mucosa.

